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(54) Title: NUCLEIC ACIDS AND PROTEINS FROM STREPTOCOCCUS GROUPS A & B

(57) Abstract: The invention provides proteins from group B streptococcus (*Streptococcus agalactiae*) and group A streptococcus (*Streptococcus pyogenes*), including amino acid sequences and the corresponding nucleotide sequences. Data are given to show that the proteins are useful antigens for vaccines, immunogenic compositions, and/or diagnostics. The proteins are also targets for antibiotics.

NUCLEIC ACIDS AND PROTEINS FROM STREPTOCOCCUS GROUPS A & B

All documents cited herein are incorporated by reference in their entirety.

TECHNICAL FIELD

This invention relates to nucleic acid and proteins from the bacteria *Streptococcus agalactiae* (GBS) and *Streptococcus pyogenes* (GAS).

BACKGROUND ART

Once thought to infect only cows, the Gram-positive bacterium *Streptococcus agalactiae* (or "group B streptococcus", abbreviated to "GBS") is now known to cause serious disease, bacteremia and meningitis, in immunocompromised individuals and in neonates. There are two types of neonatal infection. The first (early onset, usually within 5 days of birth) is manifested by bacteremia and pneumonia. It is contracted vertically as a baby passes through the birth canal. GBS colonises the vagina of about 25% of young women, and approximately 1% of infants born via a vaginal birth to colonised mothers will become infected. Mortality is between 50-70%. The second is a meningitis that occurs 10 to 60 days after birth. If pregnant women are vaccinated with type III capsule so that the infants are passively immunised, the incidence of the late onset meningitis is reduced but is not entirely eliminated.

The "B" in "GBS" refers to the Lancefield classification, which is based on the antigenicity of a carbohydrate which is soluble in dilute acid and called the C carbohydrate. Lancefield identified 13 types of C carbohydrate, designated A to O, that could be serologically differentiated. The organisms that most commonly infect humans are found in groups A, B, D, and G. Within group B, strains can be divided into 8 serotypes (Ia, Ib, Ia/c, II, III, IV, V, and VI) based on the structure of their polysaccharide capsule.

Group A streptococcus ("GAS", *S.pyogenes*) is a frequent human pathogen, estimated to be present in between 5-15% of normal individuals without signs of disease. When host defences are compromised, or when the organism is able to exert its virulence, or when it is introduced to vulnerable tissues or hosts, however, an acute infection occurs. Diseases include puerperal fever, scarlet fever, erysipelas, pharyngitis, impetigo, necrotising fasciitis, myositis and streptococcal toxic shock syndrome.

S.pyogenes is typically treated using antibiotics. Although *S.agalactiae* is inhibited by antibiotics, however, it is not killed by penicillin as easily as GAS. Prophylactic vaccination is thus preferable.

Current GBS vaccines are based on polysaccharide antigens, although these suffer from poor immunogenicity. Anti-idiotypic approaches have also been used (*e.g.* WO99/54457). There remains a need, however, for effective adult vaccines against *S.agalactiae* infection. There also remains a need for vaccines against *S.pyogenes* infection.

It is an object of the invention to provide proteins which can be used in the development of such vaccines. The proteins may also be useful for diagnostic purposes, and as targets for antibiotics.

DISCLOSURE OF THE INVENTION

The invention provides proteins comprising the *S.agalactiae* amino acid sequences disclosed in the examples, and proteins comprising the *S.pyogenes* amino acid sequences disclosed in the examples. These amino acid sequences are the even SEQ IDs between 1 and 10960.

It also provides proteins comprising amino acid sequences having sequence identity to the *S.agalactiae* amino acid sequences disclosed in the examples, and proteins comprising amino acid sequences having sequence identity to the *S.pyogenes* amino acid sequences disclosed in the examples. Depending on the particular sequence, the degree of sequence identity is preferably greater than 50% (*e.g.* 60%, 70%, 80%, 90%, 95%, 99% or more). These proteins include homologs, orthologs, allelic variants and functional mutants. Typically, 50% identity or more between two proteins is considered to be an indication of functional equivalence. Identity between proteins is preferably determined by the Smith-Waterman homology search algorithm as implemented in the MPSRCH program (Oxford Molecular), using an affine gap search with parameters *gap open penalty=12* and *gap extension penalty=1*.

Preferred proteins of the invention are GBS1 to GBS689 (see Table IV).

The invention further provides proteins comprising fragments of the *S.agalactiae* amino acid sequences disclosed in the examples, and proteins comprising fragments of the *S.pyogenes* amino acid sequences disclosed in the examples. The fragments should comprise at least *n* consecutive amino acids from the sequences and, depending on the particular sequence, *n* is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more). Preferably the fragments comprise one or more epitopes from the sequence. Other preferred fragments are (a) the N-terminal signal peptides of the proteins disclosed in the examples, (b) the proteins disclosed in the examples, but without their N-terminal signal peptides, (c) fragments common to the related GAS and GBS proteins disclosed in the examples, and (d) the proteins disclosed in the examples, but without their N-terminal amino acid residue.

The proteins of the invention can, of course, be prepared by various means (*e.g.* recombinant expression, purification from GAS or GBS, chemical synthesis *etc.*) and in various forms (*e.g.* native, fusions, glycosylated, non-glycosylated *etc.*). They are preferably prepared in substantially pure form (*i.e.* substantially free from other streptococcal or host cell proteins) or substantially isolated form. Proteins of the invention are preferably streptococcal proteins.

According to a further aspect, the invention provides antibodies which bind to these proteins. These may be polyclonal or monoclonal and may be produced by any suitable means (*e.g.* by recombinant expression). To increase compatibility with the human immune system, the antibodies may be chimeric or humanised (*e.g.* Breedveld (2000) *Lancet* 355(9205):735-740; Gorman & Clark (1990) *Semin. Immunol.* 2:457-466), or fully human antibodies may be used. The antibodies may include a detectable label (*e.g.* for diagnostic assays).

According to a further aspect, the invention provides nucleic acid comprising the *S.agalactiae* nucleotide sequences disclosed in the examples, and nucleic acid comprising the *S.pyogenes* nucleotide sequences disclosed in the examples. These nucleic acid sequences are the odd SEQ IDs between 1 and 10966.

In addition, the invention provides nucleic acid comprising nucleotide sequences having sequence identity to the *S.agalactiae* nucleotide sequences disclosed in the examples, and nucleic acid comprising nucleotide sequences having sequence identity to the *S.pyogenes* nucleotide sequences disclosed in the examples. Identity between sequences is preferably determined by the Smith-Waterman homology search algorithm as described above.

Furthermore, the invention provides nucleic acid which can hybridise to the *S.agalactiae* nucleic acid disclosed in the examples, and nucleic acid which can hybridise to the *S.pyogenes* nucleic acid disclosed in the examples preferably under 'high stringency' conditions (*e.g.* 65°C in 0.1xSSC, 0.5% SDS solution).

Nucleic acid comprising fragments of these sequences are also provided. These should comprise at least *n* consecutive nucleotides from the *S.agalactiae* or *S.pyogenes* sequences and, depending on the particular sequence, *n* is 10 or more (*e.g.* 12, 14, 15, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). The fragments may comprise sequences which are common to the related GAS and GBS sequences disclosed in the examples.

According to a further aspect, the invention provides nucleic acid encoding the proteins and protein fragments of the invention.

The invention also provides: nucleic acid comprising nucleotide sequence SEQ ID 10967; nucleic acid comprising nucleotide sequences having sequence identity to SEQ ID 10967; nucleic acid which can hybridise to SEQ ID 10967 (preferably under 'high stringency' conditions); nucleic acid comprising a fragment of at least *n* consecutive nucleotides from SEQ ID 10967, wherein *n* is 10 or more *e.g.* 12, 14, 15, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1000, 1500, 2000, 3000, 4000, 5000, 10000, 100000, 1000000 or more

Nucleic acids of the invention can be used in hybridisation reactions (*e.g.* Northern or Southern blots, or in nucleic acid microarrays or 'gene chips') and amplification reactions (*e.g.* PCR, SDA, SSSR, LCR, TMA, NASBA *etc.*) and other nucleic acid techniques.

It should also be appreciated that the invention provides nucleic acid comprising sequences complementary to those described above (*e.g.* for antisense or probing, or for use as primers).

Nucleic acid according to the invention can, of course, be prepared in many ways (*e.g.* by chemical synthesis, from genomic or cDNA libraries, from the organism itself *etc.*) and can take various forms (*e.g.* single stranded, double stranded, vectors, primers, probes, labelled *etc.*). The nucleic acid is preferably in substantially isolated form.

Nucleic acid according to the invention may be labelled *e.g.* with a radioactive or fluorescent label. This is particularly useful where the nucleic acid is to be used in nucleic acid detection techniques *e.g.* where the nucleic acid is a primer or as a probe for use in techniques such as PCR, LCR, TMA, NASBA *etc.*

In addition, the term "nucleic acid" includes DNA and RNA, and also their analogues, such as those containing modified backbones, and also peptide nucleic acids (PNA) *etc.*

According to a further aspect, the invention provides vectors comprising nucleotide sequences of the invention (*e.g.* cloning or expression vectors) and host cells transformed with such vectors.

According to a further aspect, the invention provides compositions comprising protein, antibody, and/or nucleic acid according to the invention. These compositions may be suitable as immunogenic compositions, for instance, or as diagnostic reagents, or as vaccines.

The invention also provides nucleic acid, protein, or antibody according to the invention for use as medicaments (*e.g.* as immunogenic compositions or as vaccines) or as diagnostic reagents. It also provides the use of nucleic acid, protein, or antibody according to the invention in the manufacture of: (i) a medicament for treating or preventing disease and/or infection caused by streptococcus; (ii) a diagnostic reagent for detecting the presence of streptococcus or of antibodies raised against streptococcus; and/or (iii) a reagent which can raise antibodies against streptococcus. Said streptococcus may be any species, group or strain, but is preferably *S.agalactiae*, especially serotype III or V, or *S.pyogenes*. Said disease may be bacteremia, meningitis, puerperal fever, scarlet fever, erysipelas, pharyngitis, impetigo, necrotising fasciitis, myositis or toxic shock syndrome.

The invention also provides a method of treating a patient, comprising administering to the patient a therapeutically effective amount of nucleic acid, protein, and/or antibody of the invention. The patient may either be at risk from the disease themselves or may be a pregnant woman ('maternal immunisation' *e.g.* Glezen & Alpers (1999) *Clin. Infect. Dis.* 28:219-224).

Administration of protein antigens is a preferred method of treatment for inducing immunity.

Administration of antibodies of the invention is another preferred method of treatment. This method of passive immunisation is particularly useful for newborn children or for pregnant women. This method will typically use monoclonal antibodies, which will be humanised or fully human.

The invention also provides a kit comprising primers (*e.g.* PCR primers) for amplifying a template sequence contained within a *Streptococcus* (*e.g. S.pyogenes* or *S.agalactiae*) nucleic acid sequence, the kit comprising a first primer and a second primer, wherein the first primer is substantially complementary to said template sequence and the second primer is substantially complementary to a complement of said template sequence, wherein the parts of said primers which have substantial complementarity define the termini of the template sequence to be amplified. The first primer and/or the second primer may include a detectable label (*e.g.* a fluorescent label).

The invention also provides a kit comprising first and second single-stranded oligonucleotides which allow amplification of a *Streptococcus* template nucleic acid sequence contained in a single- or double-stranded nucleic acid (or mixture thereof), wherein: (a) the first oligonucleotide comprises a primer sequence which is substantially complementary to said template nucleic acid sequence; (b) the second oligonucleotide comprises a primer sequence which is substantially complementary to the complement of said template nucleic acid sequence; (c) the first oligonucleotide and/or the second oligonucleotide comprise(s) sequence which is not compementary to said template nucleic acid; and (d) said primer sequences define the termini of the template sequence to be amplified. The non-complementary sequence(s) of feature (c) are preferably upstream of (*i.e.* 5' to) the primer sequences. One or both of these (c) sequences may comprise a restriction site (*e.g.* EP-B-0509612) or a promoter sequence (*e.g.* EP-B-0505012). The first oligonucleotide and/or the second oligonucleotide may include a detectable label (*e.g.* a fluorescent label).

The template sequence may be any part of a genome sequence (*e.g.* SEQ ID 10967). For example, it could be a rRNA gene (*e.g.* Turenne *et al.* (2000) *J. Clin. Microbiol.* 38:513-520; SEQ IDs 12018-12024 herein) or a protein-coding gene. The template sequence is preferably specific to GBS.

The invention also provides a computer-readable medium (*e.g.* a floppy disk, a hard disk, a CD-ROM, a DVD *etc.*) and/or a computer database containing one or more of the sequences in the sequence listing. The medium preferably contains SEQ ID 10967.

The invention also provides a hybrid protein represented by the formula NH_2-A-[-X-L-]$_n$-B-COOH, wherein X is a protein of the invention, L is an optional linker amino acid sequence, A is an optional N-terminal amino acid sequence, B is an optional C-terminal amino acid sequence, and n is an integer greater than 1. The value of n is between 2 and x, and the value of x is typically 3, 4, 5, 6, 7, 8, 9 or 10. Preferably n is 2, 3 or 4; it is more preferably 2 or 3; most preferably, $n = 2$. For each n instances, -X- may be the same or different. For each n instances of [-X-L-], linker amino acid sequence -L- may be present or absent. For instance, when n=2 the hybrid may be NH_2-X_1-L_1-X_2-L_2-COOH, NH_2-X_1-X_2-COOH, NH_2-X_1-L_1-X_2-COOH, NH_2-X_1-X_2-L_2-COOH, *etc.* Linker amino acid sequence(s) -L- will typically be short (*e.g.* 20 or fewer amino acids *i.e.* 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include short peptide sequences which facilitate cloning, poly-glycine linkers (*i.e.* Gly_n where n = 2, 3, 4, 5, 6, 7, 8, 9, 10 or more), and histidine tags (*i.e.* His_n where n = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable linker amino acid sequences will be apparent to those skilled in the art. -A- and -B- are optional sequences which will typically be short (*e.g.* 40 or fewer amino acids *i.e.* 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include leader sequences to direct protein trafficking, or short peptide sequences which facilitate cloning or purification (*e.g.* histidine tags *i.e.* His_n where n = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable N-terminal and C-terminal amino acid sequences will be apparent to those

skilled in the art. In some embodiments, each X will be a GBS sequence; in others, mixtures of GAS and GBS will be used.

According to further aspects, the invention provides various processes.

A process for producing proteins of the invention is provided, comprising the step of culturing a host cell of to the invention under conditions which induce protein expression.

A process for producing protein or nucleic acid of the invention is provided, wherein the protein or nucleic acid is synthesised in part or in whole using chemical means.

A process for detecting polynucleotides of the invention is provided, comprising the steps of: (a) contacting a nucleic probe according to the invention with a biological sample under hybridising conditions to form duplexes; and (b) detecting said duplexes.

A process for detecting *Streptococcus* in a biological sample (*e.g.* blood) is also provided, comprising the step of contacting nucleic acid according to the invention with the biological sample under hybridising conditions. The process may involve nucleic acid amplification (*e.g.* PCR, SDA, SSSR, LCR, TMA, NASBA *etc.*) or hybridisation (*e.g.* microarrays, blots, hybridisation with a probe in solution *etc.*). PCR detection of *Streptococcus* in clinical samples, in particular *S.pyogenes*, has been reported [see *e.g.* Louie *et al.* (2000) *CMAJ* 163:301-309; Louie *et al.* (1998) *J. Clin. Microbiol.* 36:1769-1771]. Clinical assays based on nucleic acid are described in general in Tang *et al.* (1997) *Clin. Chem.* 43:2021-2038.

A process for detecting proteins of the invention is provided, comprising the steps of: (a) contacting an antibody of the invention with a biological sample under conditions suitable for the formation of an antibody-antigen complexes; and (b) detecting said complexes.

A process for identifying an amino acid sequence is provided, comprising the step of searching for putative open reading frames or protein-coding regions within a genome sequence of *S.agalactiae*. This will typically involve *in silico* searching the sequence for an initiation codon and for an in-frame termination codon in the downstream sequence. The region between these initiation and termination codons is a putative protein-coding sequence. Typically, all six possible reading frames will be searched. Suitable software for such analysis includes ORFFINDER (NCBI), GENEMARK [Borodovsky & McIninch (1993) *Computers Chem.* 17:122-133), GLIMMER [Salzberg *et al.* (1998) *Nucleic Acids Res.* 26:544-548; Salzberg *et al.* (1999) *Genomics* 59:24-31; Delcher *et al.* (1999) *Nucleic Acids Res.* 27:4636-4641], or other software which uses Markov models [*e.g.* Shmatkov *et al.* (1999) *Bioinformatics* 15:874-876]. The invention also provides a protein comprising the identified amino acid sequence. These proteins can then expressed using conventional techniques.

The invention also provides a process for determining whether a test compound binds to a protein of the invention. If a test compound binds to a protein of the invention and this binding inhibits the life cycle of the GBS bacterium, then the test compound can be used as an antibiotic or as a lead compound for the

design of antibiotics. The process will typically comprise the steps of contacting a test compound with a protein of the invention, and determining whether the test compound binds to said protein. Preferred proteins of the invention for use in these processes are enzymes (*e.g.* tRNA synthetases), membrane transporters and ribosomal proteins. Suitable test compounds include proteins, polypeptides, carbohydrates, lipids, nucleic acids (*e.g.* DNA, RNA, and modified forms thereof), as well as small organic compounds (*e.g.* MW between 200 and 2000 Da). The test compounds may be provided individually, but will typically be part of a library (*e.g.* a combinatorial library). Methods for detecting a binding interaction include NMR, filter-binding assays, gel-retardation assays, displacement assays, surface plasmon resonance, reverse two-hybrid *etc.* A compound which binds to a protein of the invention can be tested for antibiotic activity by contacting the compound with GBS bacteria and then monitoring for inhibition of growth. The invention also provides a compound identified using these methods.

The invention also provides a composition comprising a protein or the invention and one or more of the following antigens:

- a protein antigen from *Helicobacter pylori* such as VacA, CagA, NAP, HopX, HopY [*e.g.* WO98/04702] and/or urease.
- a protein antigen from *N.meningitidis* serogroup B, such as those in WO99/24578, WO99/36544, WO99/57280, WO00/22430, Tettelin *et al.* (2000) *Science* 287:1809-1815, Pizza *et al.* (2000) *Science* 287:1816-1820 and WO96/29412, with protein '287' and derivatives being particularly preferred.
- an outer-membrane vesicle (OMV) preparation from *N.meningitidis* serogroup B, such as those disclosed in WO01/52885; Bjune *et al.* (1991) *Lancet* 338(8775):1093-1096; Fukasawa *et al.* (1999) *Vaccine* 17:2951-2958; Rosenqvist *et al.* (1998) *Dev. Biol. Stand.* 92:323-333 *etc.*
- a saccharide antigen from *N.meningitidis* serogroup A, C, W135 and/or Y, such as the oligosaccharide disclosed in Costantino *et al.* (1992) *Vaccine* 10:691-698from serogroup C [see also Costantino *et al.* (1999) *Vaccine* 17:1251-1263].
- a saccharide antigen from *Streptococcus pneumoniae* [*e.g.* Watson (2000) *Pediatr Infect Dis J* 19:331-332; Rubin (2000) *Pediatr Clin North Am* 47:269-285, v; Jedrzejas (2001) *Microbiol Mol Biol Rev* 65:187-207].
- an antigen from hepatitis A virus, such as inactivated virus [*e.g.* Bell (2000) *Pediatr Infect Dis J* 19:1187-1188; Iwarson (1995) *APMIS* 103:321-326].
- an antigen from hepatitis B virus, such as the surface and/or core antigens [*e.g.* Gerlich *et al.* (1990) *Vaccine* 8 Suppl:S63-68 & 79-80].
- an antigen from hepatitis C virus [*e.g.* Hsu *et al.* (1999) *Clin Liver Dis* 3:901-915].
- an antigen from *Bordetella pertussis*, such as pertussis holotoxin (PT) and filamentous haemagglutinin (FHA) from *B.pertussis*, optionally also in combination with pertactin and/or

agglutinogens 2 and 3 [*e.g.* Gustafsson *et al.* (1996) *N. Engl. J. Med.* 334:349-355; Rappuoli *et al.* (1991) *TIBTECH* 9:232-238].

- a diphtheria antigen, such as a diphtheria toxoid [*e.g.* chapter 3 of *Vaccines* (1988) eds. Plotkin & Mortimer. ISBN 0-7216-1946-0] *e.g.* the CRM_{197} mutant [*e.g.* Del Guidice *et al.* (1998) *Molecular Aspects of Medicine* 19:1-70].
- a tetanus antigen, such as a tetanus toxoid [*e.g.* chapter 4 of Plotkin & Mortimer].
- a saccharide antigen from *Haemophilus influenzae* B.
- an antigen from *N.gonorrhoeae* [*e.g.* WO99/24578, WO99/36544, WO99/57280].
- an antigen from *Chlamydia pneumoniae* [*e.g.* PCT/IB01/01445; Kalman *et al.* (1999) *Nature Genetics* 21:385-389; Read *et al.* (2000) *Nucleic Acids Res* 28:1397-406; Shirai *et al.* (2000) *J. Infect. Dis.* 181(Suppl 3):S524-S527; WO99/27105; WO00/27994; WO00/37494].
- an antigen from *Chlamydia trachomatis* [*e.g.* WO99/28475].
- an antigen from *Porphyromonas gingivalis* [*e.g.* Ross *et al.* (2001) *Vaccine* 19:4135-4142].
- polio antigen(s) [*e.g.* Sutter *et al.* (2000) *Pediatr Clin North Am* 47:287-308; Zimmerman & Spann (1999) *Am Fam Physician* 59:113-118, 125-126] such as IPV or OPV.
- rabies antigen(s) [*e.g.* Dreesen (1997) *Vaccine* 15 Suppl:S2-6] such as lyophilised inactivated virus [*e.g. MMWR Morb Mortal Wkly Rep* 1998 Jan 16;47(1):12, 19; RabAvert™].
- measles, mumps and/or rubella antigens [*e.g.* chapters 9, 10 & 11 of Plotkin & Mortimer].
- influenza antigen(s) [*e.g.* chapter 19 of Plotkin & Mortimer], such as the haemagglutinin and/or neuraminidase surface proteins.
- an antigen from *Moraxella catarrhalis* [*e.g.* McMichael (2000) *Vaccine* 19 Suppl 1:S101-107].
- an antigen from *Staphylococcus aureus* [*e.g.* Kuroda *et al.* (2001) *Lancet* 357(9264):1225-1240; see also pages 1218-1219].

Where a saccharide or carbohydrate antigen is included, it is preferably conjugated to a carrier protein in order to enhance immunogenicity [*e.g.* Ramsay *et al.* (2001) *Lancet* 357(9251):195-196; Lindberg (1999) *Vaccine* 17 Suppl 2:S28-36; *Conjugate Vaccines* (eds. Cruse *et al.*) ISBN 3805549326, particularly vol. 10:48-114 *etc.*]. Preferred carrier proteins are bacterial toxins or toxoids, such as diphtheria or tetanus toxoids. The CRM_{197} diphtheria toxoid is particularly preferred. Other suitable carrier proteins include the *N.meningitidis* outer membrane protein [*e.g.* EP-0372501], synthetic peptides [*e.g.* EP-0378881, EP-0427347], heat shock proteins [*e.g.* WO93/17712], pertussis proteins [*e.g.* WO98/58668; EP-0471177], protein D from *H.influenzae* [*e.g.* WO00/56360], toxin A or B from *C.difficile* [*e.g.* WO00/61761], *etc.* Any suitable conjugation reaction can be used, with any suitable linker where necessary.

Toxic protein antigens may be detoxified where necessary (*e.g.* detoxification of pertussis toxin by chemical and/or genetic means).

Where a diphtheria antigen is included in the composition it is preferred also to include tetanus antigen and pertussis antigens. Similarly, where a tetanus antigen is included it is preferred also to include diphtheria and pertussis antigens. Similarly, where a pertussis antigen is included it is preferred also to include diphtheria and tetanus antigens.

Antigens are preferably adsorbed to an aluminium salt.

Antigens in the composition will typically be present at a concentration of at least 1μg/ml each. In general, the concentration of any given antigen will be sufficient to elicit an immune response against that antigen.

The invention also provides compositions comprising two or more proteins of the present invention. The two or more proteins may comprise GBS sequences or may comprise GAS and GBS sequences.

A summary of standard techniques and procedures which may be employed to perform the invention (*e.g.* to utilise the disclosed sequences for vaccination or diagnostic purposes) follows. This summary is not a limitation on the invention but, rather, gives examples that may be used, but are not required.

General

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology, microbiology, recombinant DNA, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature *eg.* Sambrook *Molecular Cloning; A Laboratory Manual, Second Edition* (1989); *DNA Cloning, Volumes I and II* (D.N Glover ed. 1985); *Oligonucleotide Synthesis* (M.J. Gait ed, 1984); *Nucleic Acid Hybridization* (B.D. Hames & S.J. Higgins eds. 1984); *Transcription and Translation* (B.D. Hames & S.J. Higgins eds. 1984); *Animal Cell Culture* (R.I. Freshney ed. 1986); *Immobilized Cells and Enzymes* (IRL Press, 1986); B. Perbal, *A Practical Guide to Molecular Cloning* (1984); the *Methods in Enzymology* series (Academic Press, Inc.), especially volumes 154 & 155; *Gene Transfer Vectors for Mammalian Cells* (J.H. Miller and M.P. Calos eds. 1987, Cold Spring Harbor Laboratory); Mayer and Walker, eds. (1987), *Immunochemical Methods in Cell and Molecular Biology* (Academic Press, London); Scopes, (1987) *Protein Purification: Principles and Practice*, Second Edition (Springer-Verlag, N.Y.), and *Handbook of Experimental Immunology, Volumes I-IV* (D.M. Weir and C. C. Blackwell eds 1986).

Standard abbreviations for nucleotides and amino acids are used in this specification.

Definitions

A composition containing X is "substantially free of" Y when at least 85% by weight of the total X+Y in the composition is X. Preferably, X comprises at least about 90% by weight of the total of X+Y in the composition, more preferably at least about 95% or even 99% by weight.

The term "comprising" means "including" as well as "consisting" *e.g.* a composition "comprising" X may consist exclusively of X or may include something additional *e.g.* X + Y.

The term "heterologous" refers to two biological components that are not found together in nature. The components may be host cells, genes, or regulatory regions, such as promoters. Although the heterologous components are not found together in nature, they can function together, as when a promoter heterologous to a gene is operably linked to the gene. Another example is where a streptococcus sequence is heterologous to a mouse host cell. A further examples would be two epitopes from the same or different proteins which have been assembled in a single protein in an arrangement not found in nature

An "origin of replication" is a polynucleotide sequence that initiates and regulates replication of polynucleotides, such as an expression vector. The origin of replication behaves as an autonomous unit of polynucleotide replication within a cell, capable of replication under its own control. An origin of replication may be needed for a vector to replicate in a particular host cell. With certain origins of replication, an expression vector can be reproduced at a high copy number in the presence of the appropriate proteins within the cell. Examples of origins are the autonomously replicating sequences, which are effective in yeast; and the viral T-antigen, effective in COS-7 cells.

A "mutant" sequence is defined as DNA, RNA or amino acid sequence differing from but having sequence identity with the native or disclosed sequence. Depending on the particular sequence, the degree of sequence identity between the native or disclosed sequence and the mutant sequence is preferably greater than 50% (*eg.* 60%, 70%, 80%, 90%, 95%, 99% or more, calculated using the Smith-Waterman algorithm as described above). As used herein, an "allelic variant" of a nucleic acid molecule, or region, for which nucleic acid sequence is provided herein is a nucleic acid molecule, or region, that occurs essentially at the same locus in the genome of another or second isolate, and that, due to natural variation caused by, for example, mutation or recombination, has a similar but not identical nucleic acid sequence. A coding region allelic variant typically encodes a protein having similar activity to that of the protein encoded by the gene to which it is being compared. An allelic variant can also comprise an alteration in the 5' or 3' untranslated regions of the gene, such as in regulatory control regions (*eg.* see US patent 5,753,235).

Expression systems

The streptococcus nucleotide sequences can be expressed in a variety of different expression systems; for example those used with mammalian cells, baculoviruses, plants, bacteria, and yeast.

i. Mammalian Systems

Mammalian expression systems are known in the art. A mammalian promoter is any DNA sequence capable of binding mammalian RNA polymerase and initiating the downstream (3') transcription of a coding sequence (*eg.* structural gene) into mRNA. A promoter will have a transcription initiating region, which is usually placed proximal to the 5' end of the coding sequence, and a TATA box, usually located 25-30 base pairs (bp) upstream of the transcription initiation site. The TATA box is thought to direct RNA polymerase II to begin RNA synthesis at the correct site. A mammalian promoter will also contain an upstream promoter element, usually located within 100 to 200 bp upstream of the TATA box. An upstream promoter element determines the rate at which transcription is initiated and can act in either orientation [Sambrook et al. (1989) "Expression of Cloned Genes in Mammalian Cells." In *Molecular Cloning: A Laboratory Manual, 2nd ed.]*.

Mammalian viral genes are often highly expressed and have a broad host range; therefore sequences encoding mammalian viral genes provide particularly useful promoter sequences. Examples include the SV40 early promoter, mouse mammary tumor virus LTR promoter, adenovirus major late promoter (Ad MLP), and herpes simplex virus promoter. In addition, sequences derived from non-viral genes, such as the murine metallotheionein gene, also provide useful promoter sequences. Expression may be either constitutive or regulated (inducible), depending on the promoter can be induced with glucocorticoid in hormone-responsive cells.

The presence of an enhancer element (enhancer), combined with the promoter elements described above, will usually increase expression levels. An enhancer is a regulatory DNA sequence that can stimulate transcription up to 1000-fold when linked to homologous or heterologous promoters, with synthesis beginning at the normal RNA start site. Enhancers are also active when they are placed upstream or downstream from the transcription initiation site, in either normal or flipped orientation, or at a distance of more than 1000 nucleotides from the promoter [Maniatis et al. (1987) *Science 236:*1237; Alberts et al. (1989) *Molecular Biology of the Cell*, 2nd ed.]. Enhancer elements derived from viruses may be particularly useful, because they usually have a broader host range. Examples include the SV40 early gene enhancer [Dijkema et al (1985) *EMBO J. 4:*761] and the enhancer/promoters derived from the long terminal repeat (LTR) of the Rous Sarcoma Virus [Gorman et al. (1982b) *Proc. Natl. Acad. Sci. 79:*6777] and from human cytomegalovirus [Boshart et al. (1985) *Cell 41:*521]. Additionally, some enhancers are regulatable and become active only in the presence of an inducer, such as a hormone or metal ion [Sassone-Corsi and Borelli (1986) *Trends Genet. 2:*215; Maniatis et al. (1987) *Science* 236:1237].

A DNA molecule may be expressed intracellularly in mammalian cells. A promoter sequence may be directly linked with the DNA molecule, in which case the first amino acid at the N-terminus of the recombinant protein will always be a methionine, which is encoded by the ATG start codon. If desired, the N-terminus may be cleaved from the protein by *in vitro* incubation with cyanogen bromide.

Alternatively, foreign proteins can also be secreted from the cell into the growth media by creating chimeric DNA molecules that encode a fusion protein comprised of a leader sequence fragment that provides for secretion of the foreign protein in mammalian

cells. Preferably, there are processing sites encoded between the leader fragment and the foreign gene that can be cleaved either *in vivo* or *in vitro*. The leader sequence fragment usually encodes a signal peptide comprised of hydrophobic amino acids which direct the secretion of the protein from the cell. The adenovirus triparite leader is an example of a leader sequence that provides for secretion of a foreign protein in mammalian cells.

Usually, transcription termination and polyadenylation sequences recognized by mammalian cells are regulatory regions located 3' to the translation stop codon and thus, together with the promoter elements, flank the coding sequence. The 3' terminus of the mature mRNA is formed by site-specific post-transcriptional cleavage and polyadenylation [Birnstiel et al. (1985) *Cell 41*:349; Proudfoot and Whitelaw (1988) "Termination and 3' end processing of eukaryotic RNA. In *Transcription and splicing* (ed. B.D. Hames and D.M. Glover); Proudfoot (1989) *Trends Biochem. Sci. 14*:105]. These sequences direct the transcription of an mRNA which can be translated into the polypeptide encoded by the DNA. Examples of transcription terminater/polyadenylation signals include those derived from SV40 [Sambrook et al (1989) "Expression of cloned genes in cultured mammalian cells." In *Molecular Cloning: A Laboratory Manual*].

Usually, the above described components, comprising a promoter, polyadenylation signal, and transcription termination sequence are put together into expression constructs. Enhancers, introns with functional splice donor and acceptor sites, and leader sequences may also be included in an expression construct, if desired. Expression constructs are often maintained in a replicon, such as an extrachromosomal element (*eg.* plasmids) capable of stable maintenance in a host, such as mammalian cells or bacteria. Mammalian replication systems include those derived from animal viruses, which require trans-acting factors to replicate. For example, plasmids containing the replication systems of papovaviruses, such as SV40 [Gluzman (1981) *Cell 23*:175] or polyomavirus, replicate to extremely high copy number in the presence of the appropriate viral T antigen. Additional examples of mammalian replicons include those derived from bovine papillomavirus and Epstein-Barr virus. Additionally, the replicon may have two replicaton systems, thus allowing it to be maintained, for example, in mammalian cells for expression and in a prokaryotic host for cloning and amplification. Examples of such mammalian-bacteria shuttle vectors include pMT2 [Kaufman et al. (1989) *Mol. Cell. Biol. 9*:946] and pHEBO [Shimizu et al. (1986) *Mol. Cell. Biol. 6*:1074].

The transformation procedure used depends upon the host to be transformed. Methods for introduction of heterologous polynucleotides into mammalian cells are known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei.

Mammalian cell lines available as hosts for expression are known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to, Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*eg.* Hep G2), and a number of other cell lines.

ii. Baculovirus Systems

The polynucleotide encoding the protein can also be inserted into a suitable insect expression vector, and is operably linked to the control elements within that vector. Vector construction employs techniques which are known in the art. Generally, the components of the expression system include a transfer vector, usually a bacterial plasmid, which contains both a fragment of the baculovirus genome, and a convenient restriction site for insertion of the heterologous gene or genes to be expressed; a wild type baculovirus with a sequence homologous to the baculovirus-specific fragment in the transfer vector (this allows for the homologous recombination of the heterologous gene in to the baculovirus genome); and appropriate insect host cells and growth media.

After inserting the DNA sequence encoding the protein into the transfer vector, the vector and the wild type viral genome are transfected into an insect host cell where the vector and viral genome are allowed to recombine. The packaged recombinant virus is expressed and recombinant plaques are identified and purified. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *inter alia*, Invitrogen, San Diego CA ("MaxBac" kit). These techniques are generally known to those skilled in the art and fully described in Summers and Smith, *Texas Agricultural Experiment Station Bulletin No. 1555* (1987) (hereinafter "Summers and Smith").

Prior to inserting the DNA sequence encoding the protein into the baculovirus genome, the above described components, comprising a promoter, leader (if desired), coding sequence, and transcription termination sequence, are usually assembled into an intermediate transplacement construct (transfer vector). This may contain a single gene and operably linked regulatory elements; multiple genes, each with its owned set of operably linked regulatory elements; or multiple genes, regulated by the same set of regulatory elements. Intermediate transplacement constructs are often maintained in a replicon, such as an extra-chromosomal

element (*e.g.* plasmids) capable of stable maintenance in a host, such as a bacterium. The replicon will have a replication system, thus allowing it to be maintained in a suitable host for cloning and amplification.

Currently, the most commonly used transfer vector for introducing foreign genes into AcNPV is pAc373. Many other vectors, known to those of skill in the art, have also been designed. These include, for example, pVL985 (which alters the polyhedrin start codon from ATG to ATT, and which introduces a BamHI cloning site 32 basepairs downstream from the ATT; see Luckow and Summers, *Virology* (1989) *17*:31.

The plasmid usually also contains the polyhedrin polyadenylation signal (Miller et al. (1988)*Ann. Rev. Microbiol.*, *42*:177) and a prokaryotic ampicillin-resistance (*amp*) gene and origin of replication for selection and propagation in *E.coli*.

Baculovirus transfer vectors usually contain a baculovirus promoter. A baculovirus promoter is any DNA sequence capable of binding a baculovirus RNA polymerase and initiating the downstream (5' to 3') transcription of a coding sequence (*eg.* structural gene) into mRNA. A promoter will have a transcription initiation region which is usually placed proximal to the 5' end of the coding sequence. This transcription initiation region usually includes an RNA polymerase binding site and a transcription initiation site. A baculovirus transfer vector may also have a second domain called an enhancer, which, if present, is usually distal to the structural gene. Expression may be either regulated or constitutive.

Structural genes, abundantly transcribed at late times in a viral infection cycle, provide particularly useful promoter sequences. Examples include sequences derived from the gene encoding the viral polyhedron protein, Friesen et al., (1986) "The Regulation of Baculovirus Gene Expression," in: *The Molecular Biology of Baculoviruses* (ed. Walter Doerfler); EPO Publ. Nos. 127 839 and 155 476; and the gene encoding the p10 protein, Vlak et al., (1988),*J. Gen. Virol. 69*:765.

DNA encoding suitable signal sequences can be derived from genes for secreted insect or baculovirus proteins, such as the baculovirus polyhedrin gene (Carbonell et al. (1988) *Gene*, *73*:409). Alternatively, since the signals for mammalian cell posttranslational modifications (such as signal peptide cleavage, proteolytic cleavage, and phosphorylation) appear to be recognized by insect cells, and the signals required for secretion and nuclear accumulation also appear to be conserved between the invertebrate cells and vertebrate cells, leaders of non-insect origin, such as those derived from genes encoding human α-interferon, Maeda et al., (1985), *Nature 315*:592; human gastrin-releasing peptide, Lebacq-Verheyden et al., (1988), *Molec. Cell. Biol. 8*:3129; human IL-2, Smith et al., (1985) *Proc. Nat'l Acad. Sci. USA*, *82*:8404; mouse IL-3, (Miyajima et al., (1987) *Gene 58*:273; and human glucocerebrosidase, Martin et al. (1988) *DNA*, *7*:99, can also be used to provide for secretion in insects.

A recombinant polypeptide or polyprotein may be expressed intracellularly or, if it is expressed with the proper regulatory sequences, it can be secreted. Good intracellular expression of nonfused foreign proteins usually requires heterologous genes that ideally have a short leader sequence containing suitable translation initiation signals preceding an ATG start signal. If desired, methionine at the N-terminus may be cleaved from the mature protein by *in vitro* incubation with cyanogen bromide.

Alternatively, recombinant polyproteins or proteins which are not naturally secreted can be secreted from the insect cell by creating chimeric DNA molecules that encode a fusion protein comprised of a leader sequence fragment that provides for secretion of the foreign protein in insects. The leader sequence fragment usually encodes a signal peptide comprised of hydrophobic amino acids which direct the translocation of the protein into the endoplasmic reticulum.

After insertion of the DNA sequence and/or the gene encoding the expression product precursor of the protein, an insect cell host is co-transformed with the heterologous DNA of the transfer vector and the genomic DNA of wild type baculovirus -- usually by co-transfection. The promoter and transcription termination sequence of the construct will usually comprise a 2-5kb section of the baculovirus genome. Methods for introducing heterologous DNA into the desired site in the baculovirus virus are known in the art. (See Summers and Smith *supra*; Ju et al. (1987); Smith et al., *Mol. Cell. Biol.* (1983) *3*:2156; and Luckow and Summers (1989)). For example, the insertion can be into a gene such as the polyhedrin gene, by homologous double crossover recombination; insertion can also be into a restriction enzyme site engineered into the desired baculovirus gene. Miller et al., (1989), *Bioessays 4*:91.The DNA sequence, when cloned in place of the polyhedrin gene in the expression vector, is flanked both 5' and 3' by polyhedrin-specific sequences and is positioned downstream of the polyhedrin promoter.

The newly formed baculovirus expression vector is subsequently packaged into an infectious recombinant baculovirus. Homologous recombination occurs at low frequency (between about 1% and about 5%); thus, the majority of the virus produced after cotransfection is still wild-type virus. Therefore, a method is necessary to identify recombinant viruses. An advantage of the expression system is a visual screen allowing recombinant viruses to be distinguished. The polyhedrin protein, which is produced by the native virus, is produced at very high levels in the nuclei of infected cells at late times after viral infection. Accumulated polyhedrin protein forms occlusion bodies that also contain embedded particles. These occlusion bodies, up to 15 μm in size, are

highly refractile, giving them a bright shiny appearance that is readily visualized under the light microscope. Cells infected with recombinant viruses lack occlusion bodies. To distinguish recombinant virus from wild-type virus, the transfection supernatant is plaqued onto a monolayer of insect cells by techniques known to those skilled in the art. Namely, the plaques are screened under the light microscope for the presence (indicative of wild-type virus) or absence (indicative of recombinant virus) of occlusion bodies. "Current Protocols in Microbiology" Vol. 2 (Ausubel et al. eds) at 16.8 (Supp. 10, 1990); Summers and Smith, *supra*; Miller et al. (1989).

Recombinant baculovirus expression vectors have been developed for infection into several insect cells. For example, recombinant baculoviruses have been developed for, *inter alia*: *Aedes aegypti* , *Autographa californica*, *Bombyx mori*, *Drosophila melanogaster*, *Spodoptera frugiperda*, and *Trichoplusia ni* (WO 89/046699; Carbonell et al., (1985) *J. Virol. 56*:153; Wright (1986) *Nature 321*:718; Smith et al., (1983) *Mol. Cell. Biol. 3*:2156; and see generally, Fraser, *et al.* (1989) *In Vitro Cell. Dev. Biol. 25*:225).

Cells and cell culture media are commercially available for both direct and fusion expression of heterologous polypeptides in a baculovirus/expression system; cell culture technology is generally known to those skilled in the art. *See, eg.* Summers and Smith *supra.*

The modified insect cells may then be grown in an appropriate nutrient medium, which allows for stable maintenance of the plasmid(s) present in the modified insect host. Where the expression product gene is under inducible control, the host may be grown to high density, and expression induced. Alternatively, where expression is constitutive, the product will be continuously expressed into the medium and the nutrient medium must be continuously circulated, while removing the product of interest and augmenting depleted nutrients. The product may be purified by such techniques as chromatography, *eg.* HPLC, affinity chromatography, ion exchange chromatography, *etc.*; electrophoresis; density gradient centrifugation; solvent extraction, *etc.* As appropriate, the product may be further purified, as required, so as to remove substantially any insect proteins which are also present in the medium, so as to provide a product which is at least substantially free of host debris, eg. proteins, lipids and polysaccharides.

In order to obtain protein expression, recombinant host cells derived from the transformants are incubated under conditions which allow expression of the recombinant protein encoding sequence. These conditions will vary, dependent upon the host cell selected. However, the conditions are readily ascertainable to those of ordinary skill in the art, based upon what is known in the art.

iii. Plant Systems

There are many plant cell culture and whole plant genetic expression systems known in the art. Exemplary plant cellular genetic expression systems include those described in patents, such as: US 5,693,506; US 5,659,122; and US 5,608,143. Additional examples of genetic expression in plant cell culture has been described by Zenk, *Phytochemistry* 30:3861-3863 (1991). Descriptions of plant protein signal peptides may be found in addition to the references described above in Vaulcombe et al.,*Mol. Gen. Genet*. 209:33-40 (1987); Chandler et al., *Plant Molecular Biology* 3:407-418 (1984); Rogers, *J. Biol. Chem.* 260:3731-3738 (1985); Rothstein et al., *Gene* 55:353-356 (1987); Whittier et al., Nucleic Acids Research 15:2515-2535 (1987); Wirsel et al., *Molecular Microbiology* 3:3-14 (1989); Yu et al., *Gene* 122:247-253 (1992). A description of the regulation of plant gene expression by the phytohormone, gibberellic acid and secreted enzymes induced by gibberellic acid can be found in R.L. Jones and J. MacMillin, Gibberellins: in: *Advanced Plant Physiology*,. Malcolm B. Wilkins, ed., 1984 Pitman Publishing Limited, London, pp. 21-52. References that describe other metabolically-regulated genes: Sheen, *Plant Cell*, 2:1027-1038(1990); Maas et al., *EMBO J.* 9:3447-3452 (1990); Benkel and Hickey, *Proc. Natl. Acad. Sci.* 84:1337-1339 (1987).

Typically, using techniques known in the art, a desired polynucleotide sequence is inserted into an expression cassette comprising genetic regulatory elements designed for operation in plants. The expression cassette is inserted into a desired expression vector with companion sequences upstream and downstream from the expression cassette suitable for expression in a plant host. The companion sequences will be of plasmid or viral origin and provide necessary characteristics to the vector to permit the vectors to move DNA from an original cloning host, such as bacteria, to the desired plant host. The basic bacterial/plant vector construct will preferably provide a broad host range prokaryote replication origin; a prokaryote selectable marker; and, for Agrobacterium transformations, T DNA sequences for Agrobacterium-mediated transfer to plant chromosomes. Where the heterologous gene is not readily amenable to detection, the construct will preferably also have a selectable marker gene suitable for determining if a plant cell has been transformed. A general review of suitable markers, for example for the members of the grass family, is found in Wilmink and Dons, 1993, *Plant Mol. Biol. Reptr*, 11(2):165-185.

Sequences suitable for permitting integration of the heterologous sequence into the plant genome are also recommended. These might include transposon sequences and the like for homologous recombination as well as Ti sequences which permit random insertion of a heterologous expression cassette into a plant genome. Suitable prokaryote selectable markers include resistance toward antibiotics such as ampicillin or tetracycline. Other DNA sequences encoding additional functions may also be present in the vector, as is known in the art.

The nucleic acid molecules of the subject invention may be included into an expression cassette for expression of the protein(s) of interest. Usually, there will be only one expression cassette, although two or more are feasible. The recombinant expression cassette will contain in addition to the heterologous protein encoding sequence the following elements, a promoter region, plant 5' untranslated sequences, initiation codon depending upon whether or not the structural gene comes equipped with one, and a transcription and translation termination sequence. Unique restriction enzyme sites at the 5' and 3' ends of the cassette allow for easy insertion into a pre-existing vector.

A heterologous coding sequence may be for any protein relating to the present invention. The sequence encoding the protein of interest will encode a signal peptide which allows processing and translocation of the protein, as appropriate, and will usually lack any sequence which might result in the binding of the desired protein of the invention to a membrane. Since, for the most part, the transcriptional initiation region will be for a gene which is expressed and translocated during germination, by employing the signal peptide which provides for translocation, one may also provide for translocation of the protein of interest. In this way, the protein(s) of interest will be translocated from the cells in which they are expressed and may be efficiently harvested. Typically secretion in seeds are across the aleurone or scutellar epithelium layer into the endosperm of the seed. While it is not required that the protein be secreted from the cells in which the protein is produced, this facilitates the isolation and purification of the recombinant protein.

Since the ultimate expression of the desired gene product will be in a eucaryotic cell it is desirable to determine whether any portion of the cloned gene contains sequences which will be processed out as introns by the host's splicosome machinery. If so, site-directed mutagenesis of the "intron" region may be conducted to prevent losing a portion of the genetic message as a false intron code, Reed and Maniatis, *Cell* 41:95-105, 1985.

The vector can be microinjected directly into plant cells by use of micropipettes to mechanically transfer the recombinant DNA. Crossway, *Mol. Gen. Genet*, 202:179-185, 1985. The genetic material may also be transferred into the plant cell by using polyethylene glycol, Krens, et al., *Nature*, 296, 72-74, 1982. Another method of introduction of nucleic acid segments is high velocity ballistic penetration by small particles with the nucleic acid either within the matrix of small beads or particles, or on the surface, Klein, et al., *Nature*, 327, 70-73, 1987 and Knudsen and Muller, 1991, *Planta*, 185:330-336 teaching particle bombardment of barley endosperm to create transgenic barley. Yet another method of introduction would be fusion of protoplasts with other entities, either minicells, cells, lysosomes or other fusible lipid-surfaced bodies, Fraley, et al., *Proc. Natl. Acad. Sci. USA*, 79, 1859-1863, 1982.

The vector may also be introduced into the plant cells by electroporation. (Fromm et al., *Proc. Natl Acad. Sci. USA* 82:5824, 1985). In this technique, plant protoplasts are electroporated in the presence of plasmids containing the gene construct. Electrical impulses of high field strength reversibly permeabilize biomembranes allowing the introduction of the plasmids. Electroporated plant protoplasts reform the cell wall, divide, and form plant callus.

All plants from which protoplasts can be isolated and cultured to give whole regenerated plants can be transformed by the present invention so that whole plants are recovered which contain the transferred gene. It is known that practically all plants can be regenerated from cultured cells or tissues, including but not limited to all major species of sugarcane, sugar beet, cotton, fruit and other trees, legumes and vegetables. Some suitable plants include, for example, species from the genera *Fragaria*, *Lotus*, *Medicago*, *Onobrychis*, *Trifolium*, *Trigonella*, *Vigna*, *Citrus*, *Linum*, *Geranium*, *Manihot*, *Daucus*, *Arabidopsis*, *Brassica*, *Raphanus*, *Sinapis*, *Atropa*, *Capsicum*, *Datura*, *Hyoscyamus*, *Lycopersion*, *Nicotiana*, *Solanum*, *Petunia*, *Digitalis*, *Majorana*, *Cichorium*, *Helianthus*, *Lactuca*, *Bromus*, *Asparagus*, *Antirrhinum*, *Hererocallis*, *Nemesia*, *Pelargonium*, *Panicum*, *Pennisetum*, *Ranunculus*, *Senecio*, *Salpiglossis*, *Cucumis*, *Browaalia*, *Glycine*, *Lolium*, *Zea*, *Triticum*, *Sorghum*, and *Datura*.

Means for regeneration vary from species to species of plants, but generally a suspension of transformed protoplasts containing copies of the heterologous gene is first provided. Callus tissue is formed and shoots may be induced from callus and subsequently rooted. Alternatively, embryo formation can be induced from the protoplast suspension. These embryos germinate as natural embryos to form plants. The culture media will generally contain various amino acids and hormones, such as auxin and cytokinins. It is also advantageous to add glutamic acid and proline to the medium, especially for such species as corn and alfalfa. Shoots and

roots normally develop simultaneously. Efficient regeneration will depend on the medium, on the genotype, and on the history of the culture. If these three variables are controlled, then regeneration is fully reproducible and repeatable.

In some plant cell culture systems, the desired protein of the invention may be excreted or alternatively, the protein may be extracted from the whole plant. Where the desired protein of the invention is secreted into the medium, it may be collected. Alternatively, the embryos and embryoless-half seeds or other plant tissue may be mechanically disrupted to release any secreted protein between cells and tissues. The mixture may be suspended in a buffer solution to retrieve soluble proteins. Conventional protein isolation and purification methods will be then used to purify the recombinant protein. Parameters of time, temperature pH, oxygen, and volumes will be adjusted through routine methods to optimize expression and recovery of heterologous protein.

iv. Bacterial Systems

Bacterial expression techniques are known in the art. A bacterial promoter is any DNA sequence capable of binding bacterial RNA polymerase and initiating the downstream (3') transcription of a coding sequence (*eg.* structural gene) into mRNA. A promoter will have a transcription initiation region which is usually placed proximal to the 5' end of the coding sequence. This transcription initiation region usually includes an RNA polymerase binding site and a transcription initiation site. A bacterial promoter may also have a second domain called an operator, that may overlap an adjacent RNA polymerase binding site at which RNA synthesis begins. The operator permits negative regulated (inducible) transcription, as a gene repressor protein may bind the operator and thereby inhibit transcription of a specific gene. Constitutive expression may occur in the absence of negative regulatory elements, such as the operator. In addition, positive regulation may be achieved by a gene activator protein binding sequence, which, if present is usually proximal (5') to the RNA polymerase binding sequence. An example of a gene activator protein is the catabolite activator protein (CAP), which helps initiate transcription of the lac operon in Escherichia coli (*E.coli*) [Raibaud *et al.* (1984) *Annu. Rev. Genet. 18*:173]. Regulated expression may therefore be either positive or negative, thereby either enhancing or reducing transcription.

Sequences encoding metabolic pathway enzymes provide particularly useful promoter sequences. Examples include promoter sequences derived from sugar metabolizing enzymes, such as galactose, lactose (*lac*) [Chang *et al.* (1977) *Nature 198*:1056], and maltose. Additional examples include promoter sequences derived from biosynthetic enzymes such as tryptophan (*trp*) [Goeddel *et al.* (1980) *Nuc. Acids Res. 8*:4057; Yelverton *et al.* (1981) *Nucl. Acids Res. 9*:731; US patent 4,738,921; EP-A-0036776 and EP-A-0121775]. The g-laotamase (*bla*) promoter system [Weissmann (1981) "The cloning of interferon and other mistakes." In *Interferon 3* (ed. I. Gresser)], bacteriophage lambda PL [Shimatake *et al.* (1981) *Nature 292*:128] and T5 [US patent 4,689,406] promoter systems also provide useful promoter sequences.

In addition, synthetic promoters which do not occur in nature also function as bacterial promoters. For example, transcription activation sequences of one bacterial or bacteriophage promoter may be joined with the operon sequences of another bacterial or bacteriophage promoter, creating a synthetic hybrid promoter [US patent 4,551,433]. For example, the *tac* promoter is a hybrid *trp-lac* promoter comprised of both *trp* promoter and *lac* operon sequences that is regulated by the *lac* repressor [Amann *et al.* (1983) *Gene 25*:167; de Boer *et al.* (1983) *Proc. Natl. Acad. Sci. 80*:21]. Furthermore, a bacterial promoter can include naturally occurring promoters of non-bacterial origin that have the ability to bind bacterial RNA polymerase and initiate transcription. A naturally occurring promoter of non-bacterial origin can also be coupled with a compatible RNA polymerase to produce high levels of expression of some genes in prokaryotes. The bacteriophage T7 RNA polymerase/promoter system is an example of a coupled promoter system [Studier *et al.* (1986) *J. Mol. Biol. 189*:113; Tabor *et al.* (1985) *Proc Natl. Acad. Sci. 82*:1074]. In addition, a hybrid promoter can also be comprised of a bacteriophage promoter and an *E.coli* operator region (EPO-A-0 267 851).

In addition to a functioning promoter sequence, an efficient ribosome binding site is also useful for the expression of foreign genes in prokaryotes. In *E.coli*, the ribosome binding site is called the Shine-Dalgarno (SD) sequence and includes an initiation codon (ATG) and a sequence 3-9 nucleotides in length located 3-11 nucleotides upstream of the initiation codon [Shine *et al.* (1975) *Nature 254*:34]. The SD sequence is thought to promote binding of mRNA to the ribosome by the pairing of bases between the SD sequence and the 3' and of *E.coli* 16S rRNA [Steitz *et al.* (1979) "Genetic signals and nucleotide sequences in messenger RNA." In *Biological Regulation and Development: Gene Expression* (ed. R.F. Goldberger)]. To express eukaryotic genes and prokaryotic genes with weak ribosome-binding site [Sambrook *et al.* (1989) "Expression of cloned genes in Escherichia coli." In *Molecular Cloning: A Laboratory Manual*].

A DNA molecule may be expressed intracellularly. A promoter sequence may be directly linked with the DNA molecule, in which case the first amino acid at the N-terminus will always be a methionine, which is encoded by the ATG start codon. If desired, methionine at the N-terminus may be cleaved from the protein by *in vitro* incubation with cyanogen bromide or by either *in vivo* on *in vitro* incubation with a bacterial methionine N-terminal peptidase (EP-A-0 219 237).

Fusion proteins provide an alternative to direct expression. Usually, a DNA sequence encoding the N-terminal portion of an endogenous bacterial protein, or other stable protein, is fused to the 5' end of heterologous coding sequences. Upon expression, this construct will provide a fusion of the two amino acid sequences. For example, the bacteriophage lambda cell gene can be linked at the 5' terminus of a foreign gene and expressed in bacteria. The resulting fusion protein preferably retains a site for a processing enzyme (factor Xa) to cleave the bacteriophage protein from the foreign gene [Nagai *et al.* (1984) *Nature 309*:810]. Fusion proteins can also be made with sequences from the *lacZ* [Jia *et al.* (1987) *Gene 60*:197], *trpE* [Allen et al. (1987) J. Biotechnol. 5:93; Makoff *et al.* (1989) *J. Gen. Microbiol. 135*:11], and *Chey* [EP-A-0 324 647] genes. The DNA sequence at the junction of the two amino acid sequences may or may not encode a cleavable site. Another example is a ubiquitin fusion protein. Such a fusion protein is made with the ubiquitin region that preferably retains a site for a processing enzyme (*e.g.* ubiquitin specific processing-protease) to cleave the ubiquitin from the foreign protein. Through this method, native foreign protein can be isolated [Miller *et al.* (1989) *Bio/Technology 7*:698].

Alternatively, foreign proteins can also be secreted from the cell by creating chimeric DNA molecules that encode a fusion protein comprised of a signal peptide sequence fragment that provides for secretion of the foreign protein in bacteria [US patent 4,336,336]. The signal sequence fragment usually encodes a signal peptide comprised of hydrophobic amino acids which direct the secretion of the protein from the cell. The protein is either secreted into the growth media (gram-positive bacteria) or into the periplasmic space, located between the inner and outer membrane of the cell (gram-negative bacteria). Preferably there are processing sites, which can be cleaved either *in vivo* or *in vitro* encoded between the signal peptide fragment and the foreign gene.

DNA encoding suitable signal sequences can be derived from genes for secreted bacterial proteins, such as the *E.coli* outer membrane protein gene (*ompA*) [Masui *et al.* (1983), in: *Experimental Manipulation of Gene Expression*; Ghrayeb *et al.* (1984) *EMBO J. 3*:2437] and the *E.coli* alkaline phosphatase signal sequence (*phoA*) [Oka *et al.* (1985) *Proc. Natl. Acad. Sci. 82*:7212]. As an additional example, the signal sequence of the alpha-amylase gene from various Bacillus strains can be used to secrete heterologous proteins from *B. subtilis* [Palva *et al.* (1982) *Proc. Natl. Acad. Sci. USA 79*:5582; EP-A-0 244 042].

Usually, transcription termination sequences recognized by bacteria are regulatory regions located 3' to the translation stop codon, and thus together with the promoter flank the coding sequence. These sequences direct the transcription of an mRNA which can be translated into the polypeptide encoded by the DNA. Transcription termination sequences frequently include DNA sequences of about 50 nucleotides capable of forming stem loop structures that aid in terminating transcription. Examples include transcription termination sequences derived from genes with strong promoters, such as the *trp* gene in *E.coli* as well as other biosynthetic genes.

Usually, the above described components, comprising a promoter, signal sequence (if desired), coding sequence of interest, and transcription termination sequence, are put together into expression constructs. Expression constructs are often maintained in a replicon, such as an extrachromosomal element (*e.g.* plasmids) capable of stable maintenance in a host, such as bacteria. The replicon will have a replication system, thus allowing it to be maintained in a prokaryotic host either for expression or for cloning and amplification. In addition, a replicon may be either a high or low copy number plasmid. A high copy number plasmid will generally have a copy number ranging from about 5 to about 200, and usually about 10 to about 150. A host containing a high copy number plasmid will preferably contain at least about 10, and more preferably at least about 20 plasmids. Either a high or low copy number vector may be selected, depending upon the effect of the vector and the foreign protein on the host.

Alternatively, the expression constructs can be integrated into the bacterial genome with an integrating vector. Integrating vectors usually contain at least one sequence homologous to the bacterial chromosome that allows the vector to integrate. Integrations appear to result from recombinations between homologous DNA in the vector and the bacterial chromosome. For example, integrating vectors constructed with DNA from various Bacillus strains integrate into the Bacillus chromosome (EP-A- 0 127 328). Integrating vectors may also be comprised of bacteriophage or transposon sequences.

Usually, extrachromosomal and integrating expression constructs may contain selectable markers to allow for the selection of bacterial strains that have been transformed. Selectable markers can be expressed in the bacterial host and may include genes which render bacteria resistant to drugs such as ampicillin, chloramphenicol, erythromycin, kanamycin (neomycin), and tetracycline [Davies *et al.* (1978) *Annu. Rev. Microbiol. 32*:469]. Selectable markers may also include biosynthetic genes, such as those in the histidine, tryptophan, and leucine biosynthetic pathways.

Alternatively, some of the above described components can be put together in transformation vectors. Transformation vectors are usually comprised of a selectable market that is either maintained in a replicon or developed into an integrating vector, as described above.

Expression and transformation vectors, either extra-chromosomal replicons or integrating vectors, have been developed for transformation into many bacteria. For example, expression vectors have been developed for, *inter alia*, the following bacteria: Bacillus subtilis [Palva *et al.* (1982) *Proc. Natl. Acad. Sci. USA 79*:5582; EP-A-0 036 259 and EP-A-0 063 953; WO 84/04541], Escherichia coli [Shimatake *et al.* (1981) *Nature 292*:128; Amann *et al.* (1985) *Gene 40*:183; Studier *et al.* (1986) *J. Mol. Biol. 189*:113; EP-A-0 036 776,EP-A-0 136 829 and EP-A-0 136 907], Streptococcus cremoris [Powell *et al.* (1988) *Appl. Environ. Microbiol. 54*:655]; Streptococcus lividans [Powell *et al.* (1988) *Appl. Environ. Microbiol. 54*:655], Streptomyces lividans [US patent 4,745,056].

Methods of introducing exogenous DNA into bacterial hosts are well-known in the art, and usually include either the transformation of bacteria treated with $CaCl_2$ or other agents, such as divalent cations and DMSO. DNA can also be introduced into bacterial cells by electroporation. Transformation procedures usually vary with the bacterial species to be transformed. See *eg.* [Masson *et al.* (1989) *FEMS Microbiol. Lett. 60*:273; Palva *et al.* (1982) *Proc. Natl. Acad. Sci. USA 79*:5582; EP-A-0 036 259 and EP-A-0 063 953; WO 84/04541, Bacillus], [Miller *et al.* (1988) *Proc. Natl. Acad. Sci. 85*:856; Wang *et al.* (1990) *J. Bacteriol. 172*:949, Campylobacter], [Cohen *et al.* (1973) *Proc. Natl. Acad. Sci. 69*:2110; Dower *et al.* (1988) *Nucleic Acids Res. 16*:6127; Kushner (1978) "An improved method for transformation of Escherichia coli with ColE1-derived plasmids. In *Genetic Engineering: Proceedings of the International Symposium on Genetic Engineering* (eds. H.W. Boyer and S. Nicosia); Mandel *et al.* (1970) *J. Mol. Biol. 53*:159; Taketo (1988) *Biochim. Biophys. Acta 949*:318; Escherichia], [Chassy *et al.* (1987) *FEMS Microbiol. Lett. 44*:173 Lactobacillus]; [Fiedler *et al.* (1988) *Anal. Biochem 170*:38, Pseudomonas]; [Augustin *et al.* (1990) *FEMS Microbiol. Lett. 66*:203, Staphylococcus], [Barany *et al.* (1980) *J. Bacteriol. 144*:698; Harlander (1987) "Transformation of Streptococcus lactis by electroporation, in: *Streptococcal Genetics* (ed. J. Ferretti and R. Curtiss III); Perry *et al.* (1981) *Infect. Immun. 32*:1295; Powell *et al.* (1988) *Appl. Environ. Microbiol. 54*:655; Somkuti *et al.* (1987) *Proc. 4th Evr. Cong. Biotechnology 1*:412, Streptococcus].

v. Yeast Expression

Yeast expression systems are also known to one of ordinary skill in the art. A yeast promoter is any DNA sequence capable of binding yeast RNA polymerase and initiating the downstream (3') transcription of a coding sequence (*eg.* structural gene) into mRNA. A promoter will have a transcription initiation region which is usually placed proximal to the 5' end of the coding sequence. This transcription initiation region usually includes an RNA polymerase binding site (the "TATA Box") and a transcription initiation site. A yeast promoter may also have a second domain called an upstream activator sequence (UAS), which, if present, is usually distal to the structural gene. The UAS permits regulated (inducible) expression. Constitutive expression occurs in the absence of a UAS. Regulated expression may be either positive or negative, thereby either enhancing or reducing transcription.

Yeast is a fermenting organism with an active metabolic pathway, therefore sequences encoding enzymes in the metabolic pathway provide particularly useful promoter sequences. Examples include alcohol dehydrogenase (ADH) (EP-A-0 284 044), enolase, glucokinase, glucose-6-phosphate isomerase, glyceraldehyde-3-phosphate-dehydrogenase (GAP or GAPDH), hexokinase, phosphofructokinase, 3-phosphoglycerate mutase, and pyruvate kinase (PyK) (EPO-A-0 329 203). The yeast *PHO5* gene, encoding acid phosphatase, also provides useful promoter sequences [Myanohara *et al.* (1983) *Proc. Natl. Acad. Sci. USA 80*:1].

In addition, synthetic promoters which do not occur in nature also function as yeast promoters. For example, UAS sequences of one yeast promoter may be joined with the transcription activation region of another yeast promoter, creating a synthetic hybrid promoter. Examples of such hybrid promoters include the ADH regulatory sequence linked to the GAP transcription activation region (US Patent Nos. 4,876,197 and 4,880,734). Other examples of hybrid promoters include promoters which consist of the regulatory sequences of either the *ADH2*, *GAL4*, *GAL10*, OR *PHO5* genes, combined with the transcriptional activation region of a glycolytic enzyme gene such as GAP or PyK (EP-A-0 164 556). Furthermore, a yeast promoter can include naturally occurring promoters of non-yeast origin that have the ability to bind yeast RNA polymerase and initiate transcription. Examples of such promoters include, *inter alia*, [Cohen *et al.* (1980) *Proc. Natl. Acad. Sci. USA 77*:1078; Henikoff *et al.* (1981) *Nature 283*:835; Hollenberg *et al.* (1981) *Curr. Topics Microbiol. Immunol. 96*:119; Hollenberg *et al.* (1979) "The Expression of Bacterial Antibiotic Resistance Genes in the Yeast Saccharomyces cerevisiae," in: *Plasmids of Medical, Environmental and Commercial Importance* (eds. K.N. Timmis and A. Puhler); Mercerau-Puigalon *et al.* (1980) *Gene 11*:163; Panthier *et al.* (1980) *Curr. Genet. 2*:109;].

A DNA molecule may be expressed intracellularly in yeast. A promoter sequence may be directly linked with the DNA molecule, in which case the first amino acid at the N-terminus of the recombinant protein will always be a methionine, which is encoded by

the ATG start codon. If desired, methionine at the N-terminus may be cleaved from the protein by *in vitro* incubation with cyanogen bromide.

Fusion proteins provide an alternative for yeast expression systems, as well as in mammalian, baculovirus, and bacterial expression systems. Usually, a DNA sequence encoding the N-terminal portion of an endogenous yeast protein, or other stable protein, is fused to the 5' end of heterologous coding sequences. Upon expression, this construct will provide a fusion of the two amino acid sequences. For example, the yeast or human superoxide dismutase (SOD) gene, can be linked at the 5' terminus of a foreign gene and expressed in yeast. The DNA sequence at the junction of the two amino acid sequences may or may not encode a cleavable site. See *eg.* EP-A-0 196 056. Another example is a ubiquitin fusion protein. Such a fusion protein is made with the ubiquitin region that preferably retains a site for a processing enzyme (*eg.* ubiquitin-specific processing protease) to cleave the ubiquitin from the foreign protein. Through this method, therefore, native foreign protein can be isolated (*eg.* WO88/024066).

Alternatively, foreign proteins can also be secreted from the cell into the growth media by creating chimeric DNA molecules that encode a fusion protein comprised of a leader sequence fragment that provide for secretion in yeast of the foreign protein. Preferably, there are processing sites encoded between the leader fragment and the foreign gene that can be cleaved either *in vivo* or *in vitro*. The leader sequence fragment usually encodes a signal peptide comprised of hydrophobic amino acids which direct the secretion of the protein from the cell.

DNA encoding suitable signal sequences can be derived from genes for secreted yeast proteins, such as the yeast invertase gene (EP-A-0 012 873; JPO. 62,096,086) and the A-factor gene (US patent 4,588,684). Alternatively, leaders of non-yeast origin, such as an interferon leader, exist that also provide for secretion in yeast (EP-A-0 060 057).

A preferred class of secretion leaders are those that employ a fragment of the yeast alpha-factor gene, which contains both a "pre" signal sequence, and a "pro" region. The types of alpha-factor fragments that can be employed include the full-length pre-pro alpha factor leader (about 83 amino acid residues) as well as truncated alpha-factor leaders (usually about 25 to about 50 amino acid residues) (US Patents 4,546,083 and 4,870,008; EP-A-0 324 274). Additional leaders employing an alpha-factor leader fragment that provides for secretion include hybrid alpha-factor leaders made with a presequence of a first yeast, but a pro-region from a second yeast alphafactor. (*eg.* see WO 89/02463.)

Usually, transcription termination sequences recognized by yeast are regulatory regions located 3' to the translation stop codon, and thus together with the promoter flank the coding sequence. These sequences direct the transcription of an mRNA which can be translated into the polypeptide encoded by the DNA. Examples of transcription terminator sequence and other yeast-recognized termination sequences, such as those coding for glycolytic enzymes.

Usually, the above described components, comprising a promoter, leader (if desired), coding sequence of interest, and transcription termination sequence, are put together into expression constructs. Expression constructs are often maintained in a replicon, such as an extrachromosomal element (*eg.* plasmids) capable of stable maintenance in a host, such as yeast or bacteria. The replicon may have two replication systems, thus allowing it to be maintained, for example, in yeast for expression and in a prokaryotic host for cloning and amplification. Examples of such yeast-bacteria shuttle vectors include YEp24 [Botstein *et al.* (1979) *Gene 8*:17-24], pCl/1 [Brake *et al.* (1984) *Proc. Natl. Acad. Sci USA 81*:4642-4646], and YRp17 [Stinchcomb *et al.* (1982) *J. Mol. Biol. 158*:157]. In addition, a replicon may be either a high or low copy number plasmid. A high copy number plasmid will generally have a copy number ranging from about 5 to about 200, and usually about 10 to about 150. A host containing a high copy number plasmid will preferably have at least about 10, and more preferably at least about 20. Enter a high or low copy number vector may be selected, depending upon the effect of the vector and the foreign protein on the host. See *eg.* Brake *et al.*, *supra*.

Alternatively, the expression constructs can be integrated into the yeast genome with an integrating vector. Integrating vectors usually contain at least one sequence homologous to a yeast chromosome that allows the vector to integrate, and preferably contain two homologous sequences flanking the expression construct. Integrations appear to result from recombinations between homologous DNA in the vector and the yeast chromosome [Orr-Weaver *et al.* (1983) *Methods in Enzymol. 101*:228-245]. An integrating vector may be directed to a specific locus in yeast by selecting the appropriate homologous sequence for inclusion in the vector. See Orr-Weaver *et al.*, *supra*. One or more expression construct may integrate, possibly affecting levels of recombinant protein produced [Rine *et al.* (1983) *Proc. Natl. Acad. Sci. USA 80*:6750]. The chromosomal sequences included in the vector can occur either as a single segment in the vector, which results in the integration of the entire vector, or two segments homologous to adjacent segments in the chromosome and flanking the expression construct in the vector, which can result in the stable integration of only the expression construct.

Usually, extrachromosomal and integrating expression constructs may contain selectable markers to allow for the selection of yeast strains that have been transformed. Selectable markers may include biosynthetic genes that can be expressed in the yeast host, such as *ADE2*, *HIS4*, *LEU2*, *TRP1*, and *ALG7*, and the G418 resistance gene, which confer resistance in yeast cells to tunicamycin and G418, respectively. In addition, a suitable selectable marker may also provide yeast with the ability to grow in the presence of toxic compounds, such as metal. For example, the presence of *CUP1* allows yeast to grow in the presence of copper ions [Butt *et al.* (1987) *Microbiol, Rev. 51*:351].

Alternatively, some of the above described components can be put together into transformation vectors. Transformation vectors are usually comprised of a selectable marker that is either maintained in a replicon or developed into an integrating vector, as described above.

Expression and transformation vectors, either extrachromosomal replicons or integrating vectors, have been developed for transformation into many yeasts. For example, expression vectors have been developed for, *inter alia*, the following yeasts:Candida albicans [Kurtz, *et al.* (1986) *Mol. Cell. Biol. 6*:142], Candida maltosa [Kunze, *et al.* (1985) *J. Basic Microbiol. 25*:141]. Hansenula polymorpha [Gleeson, *et al.* (1986) *J. Gen. Microbiol. 132*:3459; Roggenkamp *et al.* (1986) *Mol. Gen. Genet. 202*:302], Kluyveromyces fragilis [Das, *et al.* (1984) *J. Bacteriol. 158*:1165], Kluyveromyces lactis [De Louvencourt *et al.* (1983) *J. Bacteriol. 154*:737; Van den Berg *et al.* (1990) *Bio/Technology 8*:135], Pichia guillerimondii [Kunze *et al.* (1985) *J. Basic Microbiol. 25*:141], Pichia pastoris [Cregg, *et al.* (1985) *Mol. Cell. Biol. 5*:3376; US Patent Nos. 4,837,148 and 4,929,555], Saccharomyces cerevisiae [Hinnen *et al.* (1978) *Proc. Natl. Acad. Sci. USA 75*:1929; Ito *et al.* (1983) *J. Bacteriol. 153*:163], Schizosaccharomyces pombe [Beach and Nurse (1981) *Nature 300*:706], and Yarrowia lipolytica [Davidow, *et al.* (1985) *Curr. Genet. 10*:380471 Gaillardin, *et al.* (1985) *Curr. Genet. 10*:49].

Methods of introducing exogenous DNA into yeast hosts are well-known in the art, and usually include either the transformation of spheroplasts or of intact yeast cells treated with alkali cations. Transformation procedures usually vary with the yeast species to be transformed. See *eg.* [Kurtz *et al.* (1986) *Mol. Cell. Biol. 6*:142; Kunze *et al.* (1985) *J. Basic Microbiol. 25*:141; Candida]; [Gleeson *et al.* (1986) *J. Gen. Microbiol. 132*:3459; Roggenkamp *et al.* (1986) *Mol. Gen. Genet. 202*:302; Hansenula]; [Das *et al.* (1984) *J. Bacteriol. 158*:1165; De Louvencourt *et al.* (1983) *J. Bacteriol. 154*:1165; Van den Berg *et al.* (1990) *Bio/Technology 8*:135; Kluyveromyces]; [Cregg *et al.* (1985) *Mol. Cell. Biol. 5*:3376; Kunze *et al.* (1985) *J. Basic Microbiol. 25*:141; US Patent Nos. 4,837,148 and 4,929,555; Pichia]; [Hinnen *et al.* (1978) *Proc. Natl. Acad. Sci. USA 75*;1929; Ito *et al.* (1983) *J. Bacteriol. 153*:163 Saccharomyces]; [Beach and Nurse (1981) *Nature 300*:706; Schizosaccharomyces]; [Davidow *et al.* (1985) *Curr. Genet. 10*:39; Gaillardin *et al.* (1985) *Curr. Genet. 10*:49; Yarrowia].

Antibodies

As used herein, the term "antibody" refers to a polypeptide or group of polypeptides composed of at least one antibody combining site. An "antibody combining site" is the three-dimensional binding space with an internal surface shape and charge distribution complementary to the features of an epitope of an antigen, which allows a binding of the antibody with the antigen. "Antibody" includes, for example, vertebrate antibodies, hybrid antibodies, chimeric antibodies, humanised antibodies, altered antibodies, univalent antibodies, Fab proteins, and single domain antibodies.

Antibodies against the proteins of the invention are useful for affinity chromatography, immunoassays, and distinguishing/identifying streptococcus proteins.

Antibodies to the proteins of the invention, both polyclonal and monoclonal, may be prepared by conventional methods. In general, the protein is first used to immunize a suitable animal, preferably a mouse, rat, rabbit or goat. Rabbits and goats are preferred for the preparation of polyclonal sera due to the volume of serum obtainable, and the availability of labeled anti-rabbit and anti-goat antibodies. Immunization is generally performed by mixing or emulsifying the protein in saline, preferably in an adjuvant such as Freund's complete adjuvant, and injecting the mixture or emulsion parenterally (generally subcutaneously or intramuscularly). A dose of 50-200 μg/injection is typically sufficient. Immunization is generally boosted 2-6 weeks later with one or more injections of the protein in saline, preferably using Freund's incomplete adjuvant. One may alternatively generate antibodies by in vitro immunization using methods known in the art, which for the purposes of this invention is considered equivalent to *in vivo* immunization. Polyclonal antisera is obtained by bleeding the immunized animal into a glass or plastic container, incubating the blood at 25°C for one hour, followed by incubating at 4°C for 2-18 hours. The serum is recovered by centrifugation (*eg.* 1,000*g* for 10 minutes). About 20-50 ml per bleed may be obtained from rabbits.

Monoclonal antibodies are prepared using the standard method of Kohler & Milstein [*Nature* (1975) 256:495-96], or a modification thereof. Typically, a mouse or rat is immunized as described above. However, rather than bleeding the animal to extract serum, the spleen (and optionally several large lymph nodes) is removed and dissociated into single cells. If desired, the

spleen cells may be screened (after removal of nonspecifically adherent cells) by applying a cell suspension to a plate or well coated with the protein antigen. B-cells expressing membrane-bound immunoglobulin specific for the antigen bind to the plate, and are not rinsed away with the rest of the suspension. Resulting B-cells, or all dissociated spleen cells, are then induced to fuse with myeloma cells to form hybridomas, and are cultured in a selective medium (*eg.* hypoxanthine, aminopterin, thymidine medium, "HAT"). The resulting hybridomas are plated by limiting dilution, and are assayed for production of antibodies which bind specifically to the immunizing antigen (and which do not bind to unrelated antigens). The selected MAb-secreting hybridomas are then cultured either *in vitro* (*eg.* in tissue culture bottles or hollow fiber reactors), or *in vivo* (as ascites in mice).

If desired, the antibodies (whether polyclonal or monoclonal) may be labeled using conventional techniques. Suitable labels include fluorophores, chromophores, radioactive atoms (particularly ^{32}P and ^{125}I), electron-dense reagents, enzymes, and ligands having specific binding partners. Enzymes are typically detected by their activity. For example, horseradish peroxidase is usually detected by its ability to convert 3,3',5,5'-tetramethylbenzidine (TMB) to a blue pigment, quantifiable with a spectrophotometer. "Specific binding partner" refers to a protein capable of binding a ligand molecule with high specificity, as for example in the case of an antigen and a monoclonal antibody specific therefor. Other specific binding partners include biotin and avidin or streptavidin, IgG and protein A, and the numerous receptor-ligand couples known in the art. It should be understood that the above description is not meant to categorize the various labels into distinct classes, as the same label may serve in several different modes. For example, ^{125}I may serve as a radioactive label or as an electron-dense reagent. HRP may serve as enzyme or as antigen for a MAb. Further, one may combine various labels for desired effect. For example, MAbs and avidin also require labels in the practice of this invention: thus, one might label a MAb with biotin, and detect its presence with avidin labeled with ^{125}I, or with an anti-biotin MAb labeled with HRP. Other permutations and possibilities will be readily apparent to those of ordinary skill in the art, and are considered as equivalents within the scope of the instant invention.

Pharmaceutical Compositions

Pharmaceutical compositions can comprise either polypeptides, antibodies, or nucleic acid of the invention. The pharmaceutical compositions will comprise a therapeutically effective amount of either polypeptides, antibodies, or polynucleotides of the claimed invention.

The term "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent to treat, ameliorate, or prevent a desired disease or condition, or to exhibit a detectable therapeutic or preventative effect. The effect can be detected by, for example, chemical markers or antigen levels. Therapeutic effects also include reduction in physical symptoms, such as decreased body temperature. The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent of the condition, and the therapeutics or combination of therapeutics selected for administration. Thus, it is not useful to specify an exact effective amount in advance. However, the effective amount for a given situation can be determined by routine experimentation and is within the judgement of the clinician.

For purposes of the present invention, an effective dose will be from about 0.01 mg/ kg to 50 mg/kg or 0.05 mg/kg to about 10 mg/kg of the molecule of the invention in the individual to which it is administered.

A pharmaceutical composition can also contain a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" refers to a carrier for administration of a therapeutic agent, such as antibodies or a polypeptide, genes, and other therapeutic agents. The term refers to any pharmaceutical carrier that does not itself induce the production of antibodies harmful to the individual receiving the composition, and which may be administered without undue toxicity. Suitable carriers may be large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and inactive virus particles. Such carriers are well known to those of ordinary skill in the art.

Pharmaceutically acceptable salts can be used therein, for example, mineral acid salts such as hydrochlorides, hydrobromides, phosphates, sulfates, and the like; and the salts of organic acids such as acetates, propionates, malonates, benzoates, and the like. A thorough discussion of pharmaceutically acceptable excipients is available in Remington's Pharmaceutical Sciences (Mack Pub. Co., N.J. 1991).

Pharmaceutically acceptable carriers in therapeutic compositions may contain liquids such as water, saline, glycerol and ethanol. Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present in such vehicles. Typically, the therapeutic compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection may also be prepared. Liposomes are included within the definition of a pharmaceutically acceptable carrier.

Delivery Methods

Once formulated, the compositions of the invention can be administered directly to the subject. The subjects to be treated can be animals; in particular, human subjects can be treated.

Direct delivery of the compositions will generally be accomplished by injection, either subcutaneously, intraperitoneally, intravenously or intramuscularly or delivered to the interstitial space of a tissue. The compositions can also be administered into a lesion. Other modes of administration include oral and pulmonary administration, suppositories, and transdermal or transcutaneous applications (*eg.* see WO98/20734), needles, and gene guns or hyposprays. Dosage treatment may be a single dose schedule or a multiple dose schedule.

Vaccines

Vaccines according to the invention may either be prophylactic (*ie.* to prevent infection) or therapeutic (*ie.* to treat disease after infection).

Such vaccines comprise immunising antigen(s), immunogen(s), polypeptide(s), protein(s) or nucleic acid, usually in combination with "pharmaceutically acceptable carriers," which include any carrier that does not itself induce the production of antibodies harmful to the individual receiving the composition. Suitable carriers are typically large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, lipid aggregates (such as oil droplets or liposomes), and inactive virus particles. Such carriers are well known to those of ordinary skill in the art. Additionally, these carriers may function as immunostimulating agents ("adjuvants"). Furthermore, the antigen or immunogen may be conjugated to a bacterial toxoid, such as a toxoid from diphtheria, tetanus, cholera, *H. pylori*, *etc.* pathogens.

Preferred adjuvants to enhance effectiveness of the composition include, but are not limited to: (1) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59™ (WO90/14837; Chapter 10 in *Vaccine Design – the subunit and adjuvant approach* (1995) ed. Powell & Newman), containing 5% Squalene, 0.5% Tween 80, and 0.5% Span 85 (optionally containing MTP-PE) formulated into submicron particles using a microfluidizer, (b) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-blocked polymer L121, and thr-MDP either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) Ribi™ adjuvant system (RAS), (Ribi Immunochem, Hamilton, MT) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (Detox™); (2) saponin adjuvants, such as QS21 or Stimulon™ (Cambridge Bioscience, Worcester, MA) may be used or particles generated therefrom such as ISCOMs (immunostimulating complexes), which ISCOMS may be devoid of additional detergent *e.g.* WO00/07621; (3) Complete Freund's Adjuvant (CFA) and Incomplete Freund's Adjuvant (IFA); (4) cytokines, such as interleukins (*e.g.* IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12 (WO99/44636), *etc.*), interferons (*e.g.* gamma interferon), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), *etc.*; (5) monophosphoryl lipid A (MPL) or 3-O-deacylated MPL (3dMPL) *e.g.* GB-2220221, EP-A-0689454; (6) combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions *e.g.* EP-A-0835318, EP-A-0735898, EP-A-0761231; (7) oligonucleotides comprising CpG motifs [Krieg *Vaccine* 2000, 19, 618-622; Krieg *Curr opin Mol Ther* 2001 3:15-24; Roman *et al.*, *Nat. Med.*, 1997, 3, 849-854; Weiner *et al.*, *PNAS USA*, 1997, 94, 10833-10837; Davis *et al.*, *J. Immunol.*, 1998, 160, 870-876; Chu *et al.*, *J. Exp. Med.*, 1997, 186, 1623-1631; Lipford *et al.*, *Eur. J. Immunol.*, 1997, 27, 2340-2344; Moldoveanu *et al.*, *Vaccine*, 1988, 16, 1216-1224, Krieg *et al.*, *Nature*, 1995, 374, 546-549; Klinman *et al.*, *PNAS USA*, 1996, 93, 2879-2883; Ballas *et al.*, *J. Immunol.*, 1996, 157, 1840-1845; Cowdery *et al.*, *J. Immunol.*, 1996, 156, 4570-4575; Halpern *et al.*, *Cell. Immunol.*, 1996, 167, 72-78; Yamamoto *et al.*, *Jpn. J. Cancer Res.*, 1988, 79, 866-873; Stacey *et al.*, *J. Immunol.*, 1996, 157, 2116-2122; Messina *et al.*, *J. Immunol.*, 1991, 147, 1759-1764; Yi *et al.*, *J. Immunol.*, 1996, 157, 4918-4925; Yi *et al.*, *J. Immunol.*, 1996, 157, 5394-5402; Yi *et al.*, *J. Immunol.*, 1998, 160, 4755-4761; and Yi *et al.*, *J. Immunol.*, 1998, 160, 5898-5906; International patent applications WO96/02555, WO98/16247, WO98/18810, WO98/40100, WO98/55495, WO98/37919 and WO98/52581] *i.e.* containing at least one CG dinucleotide, with 5-methylcytosine optionally being used in place of cytosine; (8) a polyoxyethylene ether or a polyoxyethylene ester *e.g.* WO99/52549; (9) a polyoxyethylene sorbitan ester surfactant in combination with an octoxynol (*e.g.* WO01/21207) or a polyoxyethylene alkyl ether or ester surfactant in combination with at least one additional non-ionic surfactant such as an octoxynol (*e.g.* WO01/21152); (10) an immunostimulatory oligonucleotide (*e.g.* a CpG oligonucleotide) and a saponin *e.g.* WO00/62800; (11) an immunostimulant and a particle of metal salt *e.g.* WO00/23105; (12) a saponin and an oil-in-water emulsion *e.g.* WO99/11241; (13) a saponin (*e.g.* QS21) + 3dMPL + IL-12 (optionally + a sterol) *e.g.* WO98/57659; (14) aluminium salts, preferably hydroxide or phosphate, but any other suitable salt may also be used (*e.g.* hydroxyphosphate, oxyhydroxide, orthophosphate, sulphate *etc.* [*e.g.* see chapters 8 & 9 of Powell & Newman]). Mixtures of different aluminium

salts may also be used. The salt may take any suitable form (*e.g.* gel, crystalline, amorphous *etc.*); (15) other substances that act as immunostimulating agents to enhance the efficacy of the composition. Aluminium salts and/or MF59™ are preferred.

As mentioned above, muramyl peptides include, but are not limited to, N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-*sn*-glycero-3-hydroxyphosphoryloxy)-ethylamine (MTP-PE), *etc.*

The immunogenic compositions (*eg.* the immunising antigen/immunogen/polypeptide/protein/ nucleic acid, pharmaceutically acceptable carrier, and adjuvant) typically will contain diluents, such as water, saline, glycerol, ethanol, etc. Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present in such vehicles.

Typically, the immunogenic compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection may also be prepared. The preparation also may be emulsified or encapsulated in liposomes for enhanced adjuvant effect, as discussed above under pharmaceutically acceptable carriers.

Immunogenic compositions used as vaccines comprise an immunologically effective amount of the antigenic or immunogenic polypeptides, as well as any other of the above-mentioned components, as needed. By "immunologically effective amount", it is meant that the administration of that amount to an individual, either in a single dose or as part of a series, is effective for treatment or prevention. This amount varies depending upon the health and physical condition of the individual to be treated, the taxonomic group of individual to be treated (*eg.* nonhuman primate, primate, *etc.*), the capacity of the individual's immune system to synthesize antibodies, the degree of protection desired, the formulation of the vaccine, the treating doctor's assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials.

The immunogenic compositions are conventionally administered parenterally, *eg.* by injection, either subcutaneously, intramuscularly, or transdermally/transcutaneously (*eg.* WO98/20734). Additional formulations suitable for other modes of administration include oral and pulmonary formulations, suppositories, and transdermal applications. Dosage treatment may be a single dose schedule or a multiple dose schedule. The vaccine may be administered in conjunction with other immunoregulatory agents.

As an alternative to protein-based vaccines, DNA vaccination may be used [*eg.* Robinson & Torres (1997) *Seminars in Immunol* 9:271-283; Donnelly *et al.* (1997) *Annu Rev Immunol* 15:617-648; later herein].

Gene Delivery Vehicles

Gene therapy vehicles for delivery of constructs including a coding sequence of a therapeutic of the invention, to be delivered to the mammal for expression in the mammal, can be administered either locally or systemically. These constructs can utilize viral or non-viral vector approaches in *in vivo* or *ex vivo* modality. Expression of such coding sequence can be induced using endogenous mammalian or heterologous promoters. Expression of the coding sequence in vivo can be either constitutive or regulated.

The invention includes gene delivery vehicles capable of expressing the contemplated nucleic acid sequences. The gene delivery vehicle is preferably a viral vector and, more preferably, a retroviral, adenoviral, adeno-associated viral (AAV), herpes viral, or alphavirus vector. The viral vector can also be an astrovirus, coronavirus, orthomyxovirus, papovavirus, paramyxovirus, parvovirus, picornavirus, poxvirus, or togavirus viral vector. See generally, Jolly (1994) *Cancer Gene Therapy* 1:51-64; Kimura (1994) *Human Gene Therapy* 5:845-852; Connelly (1995) *Human Gene Therapy* 6:185-193; and Kaplitt (1994) *Nature Genetics* 6:148-153.

Retroviral vectors are well known in the art and we contemplate that any retroviral gene therapy vector is employable in the invention, including B, C and D type retroviruses, xenotropic retroviruses (for example, NZB-X1, NZB-X2 and NZB9-1 (see O'Neill (1985) *J. Virol.* 53:160) polytropic retroviruses *eg.* MCF and MCF-MLV (see Kelly (1983) *J. Virol.* 45:291), spumaviruses and lentiviruses. See RNA Tumor Viruses, Second Edition, Cold Spring Harbor Laboratory, 1985.

Portions of the retroviral gene therapy vector may be derived from different retroviruses. For example, retrovector LTRs may be derived from a Murine Sarcoma Virus, a tRNA binding site from a Rous Sarcoma Virus, a packaging signal from a Murine Leukemia Virus, and an origin of second strand synthesis from an Avian Leukosis Virus.

These recombinant retroviral vectors may be used to generate transduction competent retroviral vector particles by introducing them into appropriate packaging cell lines (see US patent 5,591,624). Retrovirus vectors can be constructed for site-specific integration into host cell DNA by incorporation of a chimeric integrase enzyme into the retroviral particle (see WO96/37626). It is preferable that the recombinant viral vector is a replication defective recombinant virus.

Packaging cell lines suitable for use with the above-described retrovirus vectors are well known in the art, are readily prepared (see WO95/30763 and WO92/05266), and can be used to create producer cell lines (also termed vector cell lines or "VCLs") for the production of recombinant vector particles. Preferably, the packaging cell lines are made from human parent cells (eg. HT1080 cells) or mink parent cell lines, which eliminates inactivation in human serum.

Preferred retroviruses for the construction of retroviral gene therapy vectors include Avian Leukosis Virus, Bovine Leukemia, Virus, Murine Leukemia Virus, Mink-Cell Focus-Inducing Virus, Murine Sarcoma Virus, Reticuloendotheliosis Virus and Rous Sarcoma Virus. Particularly preferred Murine Leukemia Viruses include 4070A and 1504A (Hartley and Rowe (1976) *J Virol* 19:19-25), Abelson (ATCC No. VR-999), Friend (ATCC No. VR-245), Graffi, Gross (ATCC Nol VR-590), Kirsten, Harvey Sarcoma Virus and Rauscher (ATCC No. VR-998) and Moloney Murine Leukemia Virus (ATCC No. VR-190). Such retroviruses may be obtained from depositories or collections such as the American Type Culture Collection ("ATCC") in Rockville, Maryland or isolated from known sources using commonly available techniques.

Exemplary known retroviral gene therapy vectors employable in this invention include those described in patent applications GB2200651, EP0415731, EP0345242, EP0334301, WO89/02468; WO89/05349, WO89/09271, WO90/02806, WO90/07936, WO94/03622, WO93/25698, WO93/25234, WO93/11230, WO93/10218, WO91/02805, WO91/02825, WO95/07994, US 5,219,740, US 4,405,712, US 4,861,719, US 4,980,289, US 4,777,127, US 5,591,624. See also Vile (1993) *Cancer Res* 53:3860-3864; Vile (1993) *Cancer Res* 53:962-967; Ram (1993) *Cancer Res* 53 (1993) 83-88; Takamiya (1992) *J Neurosci Res* 33:493-503; Baba (1993) *J Neurosurg* 79:729-735; Mann (1983) *Cell* 33:153; Cane (1984) *Proc Natl Acad Sci* 81:6349; and Miller (1990) *Human Gene Therapy* 1.

Human adenoviral gene therapy vectors are also known in the art and employable in this invention. See, for example, Berkner (1988) *Biotechniques* 6:616 and Rosenfeld (1991) *Science* 252:431, and WO93/07283, WO93/06223, and WO93/07282. Exemplary known adenoviral gene therapy vectors employable in this invention include those described in the above referenced documents and in WO94/12649, WO93/03769, WO93/19191, WO94/28938, WO95/11984, WO95/00655, WO95/27071, WO95/29993, WO95/34671, WO96/05320, WO94/08026, WO94/11506, WO93/06223, WO94/24299, WO95/14102, WO95/24297, WO95/02697, WO94/28152, WO94/24299, WO95/09241, WO95/25807, WO95/05835, WO94/18922 and WO95/09654. Alternatively, administration of DNA linked to killed adenovirus as described in Curiel (1992) *Hum. Gene Ther.* 3:147-154 may be employed. The gene delivery vehicles of the invention also include adenovirus associated virus (AAV) vectors. Leading and preferred examples of such vectors for use in this invention are the AAV-2 based vectors disclosed in Srivastava, WO93/09239. Most preferred AAV vectors comprise the two AAV inverted terminal repeats in which the native D-sequences are modified by substitution of nucleotides, such that at least 5 native nucleotides and up to 18 native nucleotides, preferably at least 10 native nucleotides up to 18 native nucleotides, most preferably 10 native nucleotides are retained and the remaining nucleotides of the D-sequence are deleted or replaced with non-native nucleotides. The native D-sequences of the AAV inverted terminal repeats are sequences of 20 consecutive nucleotides in each AAV inverted terminal repeat (ie. there is one sequence at each end) which are not involved in HP formation. The non-native replacement nucleotide may be any nucleotide other than the nucleotide found in the native D-sequence in the same position. Other employable exemplary AAV vectors are pWP-19, pWN-1, both of which are disclosed in Nahreini (1993) *Gene* 124:257-262. Another example of such an AAV vector is psub201 (see Samulski (1987) *J. Virol.* 61:3096). Another exemplary AAV vector is the Double-D ITR vector. Construction of the Double-D ITR vector is disclosed in US Patent 5,478,745. Still other vectors are those disclosed in Carter US Patent 4,797,368 and Muzyczka US Patent 5,139,941, Chartejee US Patent 5,474,935, and Kotin WO94/288157. Yet a further example of an AAV vector employable in this invention is SSV9AFABTKneo, which contains the AFP enhancer and albumin promoter and directs expression predominantly in the liver. Its structure and construction are disclosed in Su (1996) *Human Gene Therapy* 7:463-470. Additional AAV gene therapy vectors are described in US 5,354,678, US 5,173,414, US 5,139,941, and US 5,252,479.

The gene therapy vectors of the invention also include herpes vectors. Leading and preferred examples are herpes simplex virus vectors containing a sequence encoding a thymidine kinase polypeptide such as those disclosed in US 5,288,641 and EP0176170 (Roizman). Additional exemplary herpes simplex virus vectors include HFEM/ICP6-LacZ disclosed in WO95/04139 (Wistar Institute), pHSVlac described in Geller (1988) *Science* 241:1667-1669 and in WO90/09441 and WO92/07945, HSV Us3::pgC-lacZ described in Fink (1992) *Human Gene Therapy* 3:11-19 and HSV 7134, 2 RH 105 and GAL4 described in EP 0453242 (Breakefield), and those deposited with the ATCC with accession numbers VR-977 and VR-260.

Also contemplated are alpha virus gene therapy vectors that can be employed in this invention. Preferred alpha virus vectors are Sindbis viruses vectors. Togaviruses, Semliki Forest virus (ATCC VR-67; ATCC VR-1247), Middleberg virus (ATCC

VR-370), Ross River virus (ATCC VR-373; ATCC VR-1246), Venezuelan equine encephalitis virus (ATCC VR923; ATCC VR-1250; ATCC VR-1249; ATCC VR-532), and those described in US patents 5,091,309, 5,217,879, and WO92/10578. More particularly, those alpha virus vectors described in US Serial No. 08/405,627, filed March 15, 1995,WO94/21792, WO92/10578, WO95/07994, US 5,091,309 and US 5,217,879 are employable. Such alpha viruses may be obtained from depositories or collections such as the ATCC in Rockville, Maryland or isolated from known sources using commonly available techniques. Preferably, alphavirus vectors with reduced cytotoxicity are used (see USSN 08/679640).

DNA vector systems such as eukaryotic layered expression systems are also useful for expressing the nucleic acids of the invention. See WO95/07994 for a detailed description of eukaryotic layered expression systems. Preferably, the eukaryotic layered expression systems of the invention are derived from alphavirus vectors and most preferably from Sindbis viral vectors.

Other viral vectors suitable for use in the present invention include those derived from poliovirus, for example ATCC VR-58 and those described in Evans, Nature 339 (1989) 385 and Sabin (1973) *J. Biol. Standardization* 1:115; rhinovirus, for example ATCC VR-1110 and those described in Arnold (1990) *J Cell Biochem* L401; pox viruses such as canary pox virus or vaccinia virus, for example ATCC VR-111 and ATCC VR-2010 and those described in Fisher-Hoch (1989) *Proc Natl Acad Sci* 86:317; Flexner (1989) *Ann NY Acad Sci* 569:86, Flexner (1990) *Vaccine* 8:17; in US 4,603,112 and US 4,769,330 and WO89/01973; SV40 virus, for example ATCC VR-305 and those described in Mulligan (1979) *Nature* 277:108 and Madzak (1992) *J Gen Virol* 73:1533; influenza virus, for example ATCC VR-797 and recombinant influenza viruses made employing reverse genetics techniques as described in US 5,166,057 and in Enami (1990) *Proc Natl Acad Sci* 87:3802-3805; Enami & Palese (1991) *J Virol* 65:2711-2713 and Luytjes (1989) *Cell* 59:110, (see also McMichael (1983) *NEJ Med* 309:13, and Yap (1978) *Nature* 273:238 and *Nature* (1979) 277:108); human immunodeficiency virus as described in EP-0386882 and in Buchschacher (1992) *J. Virol.* 66:2731; measles virus, for example ATCC VR-67 and VR-1247 and those described in EP-0440219; Aura virus, for example ATCC VR-368; Bebaru virus, for example ATCC VR-600 and ATCC VR-1240; Cabassou virus, for example ATCC VR-922; Chikungunya virus, for example ATCC VR-64 and ATCC VR-1241; Fort Morgan Virus, for example ATCC VR-924; Getah virus, for example ATCC VR-369 and ATCC VR-1243; Kyzylagach virus, for example ATCC VR-927; Mayaro virus, for example ATCC VR-66; Mucambo virus, for example ATCC VR-580 and ATCC VR-1244; Ndumu virus, for example ATCC VR-371; Pixuna virus, for example ATCC VR-372 and ATCC VR-1245; Tonate virus, for example ATCC VR-925; Triniti virus, for example ATCC VR-469; Una virus, for example ATCC VR-374; Whataroa virus, for example ATCC VR-926; Y-62-33 virus, for example ATCC VR-375; O'Nyong virus, Eastern encephalitis virus, for example ATCC VR-65 and ATCC VR-1242; Western encephalitis virus, for example ATCC VR-70, ATCC VR-1251, ATCC VR-622 and ATCC VR-1252; and coronavirus, for example ATCC VR-740 and those described in Hamre (1966) *Proc Soc Exp Biol Med* 121:190.

Delivery of the compositions of this invention into cells is not limited to the above mentioned viral vectors. Other delivery methods and media may be employed such as, for example, nucleic acid expression vectors, polycationic condensed DNA linked or unlinked to killed adenovirus alone, for example see US Serial No. 08/366,787, filed December 30, 1994 and Curiel (1992) *Hum Gene Ther* 3:147-154 ligand linked DNA, for example see Wu (1989) *J Biol Chem* 264:16985-16987, eucaryotic cell delivery vehicles cells, for example see US Serial No.08/240,030, filed May 9, 1994, and US Serial No. 08/404,796, deposition of photopolymerized hydrogel materials, hand-held gene transfer particle gun, as described in US Patent 5,149,655, ionizing radiation as described in US5,206,152 and in WO92/11033, nucleic charge neutralization or fusion with cell membranes. Additional approaches are described in Philip (1994) *Mol Cell Biol* 14:2411-2418 and in Woffendin (1994) *Proc Natl Acad Sci* 91:1581-1585.

Particle mediated gene transfer may be employed, for example see US Serial No. 60/023,867. Briefly, the sequence can be inserted into conventional vectors that contain conventional control sequences for high level expression, and then incubated with synthetic gene transfer molecules such as polymeric DNA-binding cations like polylysine, protamine, and albumin, linked to cell targeting ligands such as asialoorosomucoid, as described in Wu & Wu (1987) *J. Biol. Chem.* 262:4429-4432, insulin as described in Hucked (1990) *Biochem Pharmacol* 40:253-263, galactose as described in Plank (1992) *Bioconjugate Chem* 3:533-539, lactose or transferrin.

Naked DNA may also be employed. Exemplary naked DNA introduction methods are described in WO 90/11092 and US 5,580,859. Uptake efficiency may be improved using biodegradable latex beads. DNA coated latex beads are efficiently transported into cells after endocytosis initiation by the beads. The method may be improved further by treatment of the beads to increase hydrophobicity and thereby facilitate disruption of the endosome and release of the DNA into the cytoplasm.

Liposomes that can act as gene delivery vehicles are described in US 5,422,120, WO95/13796, WO94/23697, WO91/14445 and EP-524,968. As described in USSN. 60/023,867, on non-viral delivery, the nucleic acid sequences encoding a polypeptide

can be inserted into conventional vectors that contain conventional control sequences for high level expression, and then be incubated with synthetic gene transfer molecules such as polymeric DNA-binding cations like polylysine, protamine, and albumin, linked to cell targeting ligands such as asialoorosomucoid, insulin, galactose, lactose, or transferrin. Other delivery systems include the use of liposomes to encapsulate DNA comprising the gene under the control of a variety of tissue-specific or ubiquitously-active promoters. Further non-viral delivery suitable for use includes mechanical delivery systems such as the approach described in Woffendin *et al* (1994) *Proc. Natl. Acad. Sci. USA* 91(24):11581-11585. Moreover, the coding sequence and the product of expression of such can be delivered through deposition of photopolymerized hydrogel materials. Other conventional methods for gene delivery that can be used for delivery of the coding sequence include, for example, use of hand-held gene transfer particle gun, as described in US 5,149,655; use of ionizing radiation for activating transferred gene, as described in US 5,206,152 and WO92/11033

Exemplary liposome and polycationic gene delivery vehicles are those described in US 5,422,120 and 4,762,915; in WO 95/13796; WO94/23697; and WO91/14445; in EP-0524968; and in Stryer, Biochemistry, pages 236-240 (1975) W.H. Freeman, San Francisco; Szoka (1980) *Biochem Biophys Acta* 600:1; Bayer (1979) *Biochem Biophys Acta* 550:464; Rivnay (1987) *Meth Enzymol* 149:119; Wang (1987) *Proc Natl Acad Sci* 84:7851; Plant (1989) *Anal Biochem* 176:420.

A polynucleotide composition can comprises therapeutically effective amount of a gene therapy vehicle, as the term is defined above. For purposes of the present invention, an effective dose will be from about 0.01 mg/ kg to 50 mg/kg or 0.05 mg/kg to about 10 mg/kg of the DNA constructs in the individual to which it is administered.

Delivery Methods

Once formulated, the polynucleotide compositions of the invention can be administered (1) directly to the subject; (2) delivered *ex vivo*, to cells derived from the subject; or (3) *in vitro* for expression of recombinant proteins. The subjects to be treated can be mammals or birds. Also, human subjects can be treated.

Direct delivery of the compositions will generally be accomplished by injection, either subcutaneously, intraperitoneally, intravenously or intramuscularly or delivered to the interstitial space of a tissue. The compositions can also be administered into a lesion. Other modes of administration include oral and pulmonary administration, suppositories, and transdermal or transcutaneous applications (*eg.* see WO98/20734), needles, and gene guns or hyposprays. Dosage treatment may be a single dose schedule or a multiple dose schedule.

Methods for the *ex vivo* delivery and reimplantation of transformed cells into a subject are known in the art and described in *eg.* WO93/14778. Examples of cells useful in ex vivo applications include, for example, stem cells, particularly hematopoetic, lymph cells, macrophages, dendritic cells, or tumor cells.

Generally, delivery of nucleic acids for both *ex vivo* and *in vitro* applications can be accomplished by the following procedures, for example, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei, all well known in the art.

Polynucleotide and polypeptide pharmaceutical compositions

In addition to the pharmaceutically acceptable carriers and salts described above, the following additional agents can be used with polynucleotide and/or polypeptide compositions.

A.Polypeptides

One example are polypeptides which include, without limitation: asioloorosomucoid (ASOR); transferrin; asialoglycoproteins; antibodies; antibody fragments; ferritin; interleukins; interferons, granulocyte, macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor (M-CSF), stem cell factor and erythropoietin. Viral antigens, such as envelope proteins, can also be used. Also, proteins from other invasive organisms, such as the 17 amino acid peptide from the circumsporozoite protein of plasmodium falciparum known as RII.

B.Hormones, Vitamins, *etc.*

Other groups that can be included are, for example: hormones, steroids, androgens, estrogens, thyroid hormone, or vitamins, folic acid.

C.Polyalkylenes, Polysaccharides, *etc.*

Also, polyalkylene glycol can be included with the desired polynucleotides/polypeptides. In a preferred embodiment, the polyalkylene glycol is polyethlylene glycol. In addition, mono-, di-, or polysaccharides can be included. In a preferred embodiment of this aspect, the polysaccharide is dextran or DEAE-dextran. Also, chitosan and poly(lactide-co-glycolide)

D.Lipids, and Liposomes

The desired polynucleotide/polypeptide can also be encapsulated in lipids or packaged in liposomes prior to delivery to the subject or to cells derived therefrom.

Lipid encapsulation is generally accomplished using liposomes which are able to stably bind or entrap and retain nucleic acid. The ratio of condensed polynucleotide to lipid preparation can vary but will generally be around 1:1 (mg DNA:micromoles lipid), or more of lipid. For a review of the use of liposomes as carriers for delivery of nucleic acids, see, Hug and Sleight (1991) *Biochim. Biophys. Acta.* 1097:1-17; Straubinger (1983) *Meth. Enzymol.* 101:512-527.

Liposomal preparations for use in the present invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner (1987) *Proc. Natl. Acad. Sci. USA* 84:7413-7416); mRNA (Malone (1989) *Proc. Natl. Acad. Sci. USA* 86:6077-6081); and purified transcription factors (Debs (1990) *J. Biol. Chem.* 265:10189-10192), in functional form.

Cationic liposomes are readily available. For example, N[1-2,3-dioleyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, NY. (See, also, Felgner *supra*). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boerhinger). Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, *eg.* Szoka (1978) *Proc. Natl. Acad. Sci. USA* 75:4194-4198; WO90/11092 for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes.

Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, AL), or can be easily prepared using readily available materials. Such materials include phosphatidyl choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

The liposomes can comprise multilammelar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs). The various liposome-nucleic acid complexes are prepared using methods known in the art. See *eg.* Straubinger (1983) *Meth. Immunol.* 101:512-527; Szoka (1978) *Proc. Natl. Acad. Sci. USA* 75:4194-4198; Papahadjopoulos (1975) *Biochim. Biophys. Acta* 394:483; Wilson (1979) *Cell* 17:77); Deamer & Bangham (1976) *Biochim. Biophys. Acta* 443:629; Ostro (1977) *Biochem. Biophys. Res. Commun.* 76:836; Fraley (1979) *Proc. Natl. Acad. Sci. USA* 76:3348); Enoch & Strittmatter (1979) *Proc. Natl. Acad. Sci. USA* 76:145; Fraley (1980) *J. Biol. Chem.* (1980) 255:10431; Szoka & Papahadjopoulos (1978) *Proc. Natl. Acad. Sci. USA* 75:145; and Schaefer-Ridder (1982) *Science* 215:166.

E.Lipoproteins

In addition, lipoproteins can be included with the polynucleotide/polypeptide to be delivered. Examples of lipoproteins to be utilized include: chylomicrons, HDL, IDL, LDL, and VLDL. Mutants, fragments, or fusions of these proteins can also be used. Also, modifications of naturally occurring lipoproteins can be used, such as acetylated LDL. These lipoproteins can target the delivery of polynucleotides to cells expressing lipoprotein receptors. Preferably, if lipoproteins are including with the polynucleotide to be delivered, no other targeting ligand is included in the composition.

Naturally occurring lipoproteins comprise a lipid and a protein portion. The protein portion are known as apoproteins. At the present, apoproteins A, B, C, D, and E have been isolated and identified. At least two of these contain several proteins, designated by Roman numerals, AI, AII, AIV; CI, CII, CIII.

A lipoprotein can comprise more than one apoprotein. For example, naturally occurring chylomicrons comprises of A, B, C & E, over time these lipoproteins lose A and acquire C & E. VLDL comprises A, B, C & E apoproteins, LDL comprises apoprotein B; and HDL comprises apoproteins A, C, & E.

The amino acid of these apoproteins are known and are described in, for example, Breslow (1985) Annu Rev. Biochem 54:699; Law (1986) Adv. Exp Med. Biol. 151:162; Chen (1986) J Biol Chem 261:12918; Kane (1980) Proc Natl Acad Sci USA 77:2465; and Utermann (1984) Hum Genet 65:232.

Lipoproteins contain a variety of lipids including, triglycerides, cholesterol (free and esters), and phospholipids. The composition of the lipids varies in naturally occurring lipoproteins. For example, chylomicrons comprise mainly triglycerides. A more detailed description of the lipid content of naturally occurring lipoproteins can be found, for example, in *Meth. Enzymol.* 128 (1986). The composition of the lipids are chosen to aid in conformation of the apoprotein for receptor binding activity. The composition of lipids can also be chosen to facilitate hydrophobic interaction and association with the polynucleotide binding molecule.

Naturally occurring lipoproteins can be isolated from serum by ultracentrifugation, for instance. Such methods are described in *Meth. Enzymol. (supra)*; Pitas (1980) *J. Biochem.* 255:5454-5460 and Mahey (1979) *J Clin. Invest* 64:743-750. Lipoproteins can also be produced by *in vitro* or recombinant methods by expression of the apoprotein genes in a desired host cell. See, for example, Atkinson (1986) *Annu Rev Biophys Chem* 15:403 and Radding (1958) *Biochim Biophys Acta* 30: 443. Lipoproteins can also be purchased from commercial suppliers, such as Biomedical Techniologies, Inc., Stoughton, MA, USA. Further description of lipoproteins can be found in WO98/06437..

F.Polycationic Agents

Polycationic agents can be included, with or without lipoprotein, in a composition with the desired polynucleotide/polypeptide to be delivered.

Polycationic agents, typically, exhibit a net positive charge at physiological relevant pH and are capable of neutralizing the electrical charge of nucleic acids to facilitate delivery to a desired location. These agents have both in vitro, ex vivo, and in vivo applications. Polycationic agents can be used to deliver nucleic acids to a living subject either intramuscularly, subcutaneously, *etc.*

The following are examples of useful polypeptides as polycationic agents: polylysine, polyarginine, polyornithine, and protamine. Other examples include histones, protamines, human serum albumin, DNA binding proteins, non-histone chromosomal proteins, coat proteins from DNA viruses, such as (X174, transcriptional factors also contain domains that bind DNA and therefore may be useful as nucleic aid condensing agents. Briefly, transcriptional factors such as C/CEBP, cjun, c-fos, AP-1, AP-2, AP-3, CPF, Prot-1, Sp-1, Oct-1, Oct-2, CREP, and TFIID contain basic domains that bind DNA sequences.

Organic polycationic agents include: spermine, spermidine, and purtrescine.

The dimensions and of the physical properties of a polycationic agent can be extrapolated from the list above, to construct other polypeptide polycationic agents or to produce synthetic polycationic agents.

Synthetic polycationic agents which are useful include, for example, DEAE-dextran, polybrene. Lipofectin™, and lipofectAMINE™ are monomers that form polycationic complexes when combined with polynucleotides/polypeptides.

Immunodiagnostic Assays

Streptococcus antigens of the invention can be used in immunoassays to detect antibody levels (or, conversely, anti-streptococcus antibodies can be used to detect antigen levels). Immunoassays based on well defined, recombinant antigens can be developed to replace invasive diagnostics methods. Antibodies to streptococcus proteins within biological samples, including for example, blood or serum samples, can be detected. Design of the immunoassays is subject to a great deal of variation, and a variety of these are known in the art. Protocols for the immunoassay may be based, for example, upon competition, or direct reaction, or sandwich type assays. Protocols may also, for example, use solid supports, or may be by immunoprecipitation. Most assays involve the use of labeled antibody or polypeptide; the labels may be, for example, fluorescent, chemiluminescent, radioactive, or dye molecules. Assays which amplify the signals from the probe are also known; examples of which are assays which utilize biotin and avidin, and enzyme-labeled and mediated immunoassays, such as ELISA assays.

Kits suitable for immunodiagnosis and containing the appropriate labeled reagents are constructed by packaging the appropriate materials, including the compositions of the invention, in suitable containers, along with the remaining reagents and materials (for example, suitable buffers, salt solutions, *etc.*) required for the conduct of the assay, as well as suitable set of assay instructions.

Nucleic Acid Hybridisation

"Hybridization" refers to the association of two nucleic acid sequences to one another by hydrogen bonding. Typically, one sequence will be fixed to a solid support and the other will be free in solution. Then, the two sequences will be placed in contact with one another under conditions that favor hydrogen bonding. Factors that affect this bonding include: the type and volume of solvent; reaction temperature; time of hybridization; agitation; agents to block the non-specific attachment of the liquid phase sequence to the solid support (Denhardt's reagent or BLOTTO); concentration of the sequences; use of compounds to increase the rate of association of sequences (dextran sulfate or polyethylene glycol); and the stringency of the washing conditions following hybridization. See Sambrook *et al.* [*supra*] Volume 2, chapter 9, pages 9.47 to 9.57.

"Stringency" refers to conditions in a hybridization reaction that favor association of very similar sequences over sequences that differ. For example, the combination of temperature and salt concentration should be chosen that is approximately 120 to 200°C below the calculated Tm of the hybrid under study. The temperature and salt conditions can often be determined empirically in preliminary experiments in which samples of genomic DNA immobilized on filters are hybridized to the sequence of interest and then washed under conditions of different stringencies. See Sambrook *et al.* at page 9.50.

Variables to consider when performing, for example, a Southern blot are (1) the complexity of the DNA being blotted and (2) the homology between the probe and the sequences being detected. The total amount of the fragment(s) to be studied can vary a magnitude of 10, from 0.1 to 1µg for a plasmid or phage digest to 10^{-9} to 10^{-8} g for a single copy gene in a highly complex eukaryotic genome. For lower complexity polynucleotides, substantially shorter blotting, hybridization, and exposure times, a smaller amount of starting polynucleotides, and lower specific activity of probes can be used. For example, a single-copy yeast gene can be detected with an exposure time of only 1 hour starting with 1 µg of yeast DNA, blotting for two hours, and hybridizing for 4-8 hours with a probe of 10^8 cpm/µg. For a single-copy mammalian gene a conservative approach would start with 10 µg of DNA, blot overnight, and hybridize overnight in the presence of 10% dextran sulfate using a probe of greater than 10^8 cpm/µg, resulting in an exposure time of ~24 hours.

Several factors can affect the melting temperature (Tm) of a DNA-DNA hybrid between the probe and the fragment of interest, and consequently, the appropriate conditions for hybridization and washing. In many cases the probe is not 100% homologous to the fragment. Other commonly encountered variables include the length and total G+C content of the hybridizing sequences and the ionic strength and formamide content of the hybridization buffer. The effects of all of these factors can be approximated by a single equation:

$$Tm = 81 + 16.6(\log_{10}Ci) + 0.4[\%(G + C)] - 0.6(\%formamide) - 600/n - 1.5(\%mismatch).$$

where Ci is the salt concentration (monovalent ions) and n is the length of the hybrid in base pairs (slightly modified from Meinkoth & Wahl (1984) *Anal. Biochem.* 138: 267-284).

In designing a hybridization experiment, some factors affecting nucleic acid hybridization can be conveniently altered. The temperature of the hybridization and washes and the salt concentration during the washes are the simplest to adjust. As the temperature of the hybridization increases (*ie.* stringency), it becomes less likely for hybridization to occur between strands that are nonhomologous, and as a result, background decreases. If the radiolabeled probe is not completely homologous with the immobilized fragment (as is frequently the case in gene family and interspecies hybridization experiments), the hybridization temperature must be reduced, and background will increase. The temperature of the washes affects the intensity of the hybridizing band and the degree of background in a similar manner. The stringency of the washes is also increased with decreasing salt concentrations.

In general, convenient hybridization temperatures in the presence of 50% formamide are 42°C for a probe with is 95% to 100% homologous to the target fragment, 37°C for 90% to 95% homology, and 32°C for 85% to 90% homology. For lower homologies, formamide content should be lowered and temperature adjusted accordingly, using the equation above. If the homology between the probe and the target fragment are not known, the simplest approach is to start with both hybridization and wash conditions which are nonstringent. If non-specific bands or high background are observed after autoradiography, the filter can be washed at high stringency and reexposed. If the time required for exposure makes this approach impractical, several hybridization and/or washing stringencies should be tested in parallel.

Nucleic Acid Probe Assays

Methods such as PCR, branched DNA probe assays, or blotting techniques utilizing nucleic acid probes according to the invention can determine the presence of cDNA or mRNA. A probe is said to "hybridize" with a sequence of the invention if it can form a duplex or double stranded complex, which is stable enough to be detected.

The nucleic acid probes will hybridize to the streptococcus nucleotide sequences of the invention (including both sense and antisense strands). Though many different nucleotide sequences will encode the amino acid sequence, the native streptococcus sequence is preferred because it is the actual sequence present in cells. mRNA represents a coding sequence and so a probe should be complementary to the coding sequence; single-stranded cDNA is complementary to mRNA, and so a cDNA probe should be complementary to the non-coding sequence.

The probe sequence need not be identical to the streptococcus sequence (or its complement) — some variation in the sequence and length can lead to increased assay sensitivity if the nucleic acid probe can form a duplex with target nucleotides, which can be detected. Also, the nucleic acid probe can include additional nucleotides to stabilize the formed duplex. Additional streptococcus sequence may also be helpful as a label to detect the formed duplex. For example, a non-complementary nucleotide sequence

may be attached to the 5' end of the probe, with the remainder of the probe sequence being complementary to a streptococcus sequence. Alternatively, non-complementary bases or longer sequences can be interspersed into the probe, provided that the probe sequence has sufficient complementarity with the a streptococcus sequence in order to hybridize therewith and thereby form a duplex which can be detected.

The exact length and sequence of the probe will depend on the hybridization conditions (*e.g.* temperature, salt condition *etc.*). For example, for diagnostic applications, depending on the complexity of the analyte sequence, the nucleic acid probe typically contains at least 10-20 nucleotides, preferably 15-25, and more preferably at least 30 nucleotides, although it may be shorter than this. Short primers generally require cooler temperatures to form sufficiently stable hybrid complexes with the template.

Probes may be produced by synthetic procedures, such as the triester method of Matteucci *et al.* [*J. Am. Chem. Soc.* (1981) 103:3185], or according to Urdea *et al.* [*Proc. Natl. Acad. Sci. USA* (1983) 80: 7461], or using commercially available automated oligonucleotide synthesizers.

The chemical nature of the probe can be selected according to preference. For certain applications, DNA or RNA are appropriate. For other applications, modifications may be incorporated *eg.* backbone modifications, such as phosphorothioates or methylphosphonates, can be used to increase *in vivo* half-life, alter RNA affinity, increase nuclease resistance *etc.* [*eg.* see Agrawal & Iyer (1995) *Curr Opin Biotechnol* 6:12-19; Agrawal (1996) *TIBTECH* 14:376-387]; analogues such as peptide nucleic acids may also be used [*eg.* see Corey (1997) *TIBTECH* 15:224-229; Buchardt *et al.* (1993) *TIBTECH* 11:384-386].

Alternatively, the polymerase chain reaction (PCR) is another well-known means for detecting small amounts of target nucleic acid. The assay is described in Mullis *et al.* [*Meth. Enzymol.* (1987) 155:335-350] & US patents 4,683,195 & 4,683,202. Two "primer" nucleotides hybridize with the target nucleic acids and are used to prime the reaction. The primers can comprise sequence that does not hybridize to the sequence of the amplification target (or its complement) to aid with duplex stability or, for example, to incorporate a convenient restriction site. Typically, such sequence will flank the desired streptococcus sequence.

A thermostable polymerase creates copies of target nucleic acids from the primers using the original target nucleic acids as a template. After a threshold amount of target nucleic acids are generated by the polymerase, they can be detected by more traditional methods, such as Southern blots. When using the Southern blot method, the labelled probe will hybridize to the streptococcus sequence (or its complement).

Also, mRNA or cDNA can be detected by traditional blotting techniques described in Sambrook *et al* [*supra*]. mRNA, or cDNA generated from mRNA using a polymerase enzyme, can be purified and separated using gel electrophoresis. The nucleic acids on the gel are then blotted onto a solid support, such as nitrocellulose. The solid support is exposed to a labelled probe and then washed to remove any unhybridized probe. Next, the duplexes containing the labeled probe are detected. Typically, the probe is labelled with a radioactive moiety.

BRIEF DESCRIPTION OF DRAWINGS

Figures 1 to **85**, **119** to **188**, **238** and **239** show SDS-PAGE analysis of total cell extracts from cultures of recombinant *E.coli* expressing GBS proteins of the invention. Lane 1 in each gel (except for Figure 185) contains molecular weight markers. These are 94, 67, 43, 30, 20.1 & 14.4 kDa (except for Figures 7, 8, 10, 11, 13, 14, 15 and 119-170, which use 250, 150, 100, 75, 50, 37, 25, 15 & 10 kDa).

Figure 86A shows the pDEST15 vector and **Figure 86B** shows the pDEST17-1 vector.

Figures 88 to **118** and **247** to **319** show protein characterisation data for various proteins of the invention.

Figures 189 to **237** and **240** to **246** show SDS-PAGE analysis of purified GBS proteins of the invention. The left-hand lane contains molecular weight markers. These are 94, 67, 43, 30, 20.1 & 14.4 kDa.

MODES FOR CARRYING OUT THE INVENTION

The following examples describe nucleic acid sequences which have been identified in *Streptococcus*, along with their inferred translation products. The examples are generally in the following format:

- a nucleotide sequence which has been identified in *Streptococcus*
- the inferred translation product of this sequence
- a computer analysis (*e.g.* PSORT output) of the translation product, indicating antigenicity

Most examples describe nucleotide sequences from *S.agalactiae*. The specific strain which was sequenced was from serotype V, and is a clinical strain isolated in Italy which expresses the R antigen (ISS/Rome/Italy collection, strain.2603 V/R). For several of these examples, the corresponding sequences from *S.pyogenes* are also given. Where GBS and GAS show homology in this way, there is conservation between species which suggests an essential function and also gives good cross-species reactivity.

In contrast, several examples describe nucleotide sequences from GAS for which no homolog in GBS has been identified. This lack of homology gives molecules which are useful for distinguishing GAS from GBS and for making GAS-specific products. The same is true for GBS sequences which lack GAS homologs *e.g.* these are useful for making GBS-specific products.

The examples typically include details of homology to sequences in the public databases. Proteins that are similar in sequence are generally similar in both structure and function, and the homology often indicates a common evolutionary origin. Comparison with sequences of proteins of known function is widely used as a guide for the assignment of putative protein function to a new sequence and has proved particularly useful in whole-genome analyses.

Various tests can be used to assess the *in vivo* immunogenicity of the proteins identified in the examples. For example, the proteins can be expressed recombinantly and used to screen patient sera by immunoblot. A positive reaction between the protein and patient serum indicates that the patient has previously mounted an immune response to the protein in question *i.e.* the protein is an immunogen. This method can also be used to identify immunodominant proteins. The mouse model used in the examples can also be used.

The recombinant protein can also be conveniently used to prepare antibodies *e.g.* in a mouse. These can be used for direct confirmation that a protein is located on the cell-surface. Labelled antibody (*e.g.* fluorescent labelling for FACS) can be incubated with intact bacteria and the presence of label on the bacterial surface confirms the location of the protein.

For many GBS proteins, the following data are given:

- SDS-PAGE analysis of total recombinant *E.coli* cell extracts for GBS protein expression
- SDS-PAGE analysis after the protein purification

- Western-blot analysis of GBS total cell extract using antisera raised against recombinant proteins
- FACS and ELISA analysis against GBS using antisera raise against recombinant proteins
- Results of the *in vivo* passive protection assay

Details of experimental techniques used are presented below:

Sequence analysis

Open reading frames (ORFs) within nucleotide sequences were predicted using the GLIMMER program [Salzberg *et al.* (1998) *Nucleic Acids Res* 26:544-8]. Where necessary, start codons were modified and corrected manually on the basis of the presence of ribosome-binding sites and promoter regions on the upstream DNA sequence.

ORFs were then screened against the non-redundant protein databases using the programs BLASTp [Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410] and PRAZE, a modification of the Smith-Waterman algorithm [Smith & Waterman (1981) *J Mol Biol* 147:195-7; see Fleischmann *et al* (1995) *Science* 269:496-512].

Leader peptides within the ORFs were located using three different approaches: (i) PSORT [Nakai (1991) *Bull. Inst. Chem. Res., Kyoto Univ.* 69:269-291; Horton & Nakai (1996) *Intellig. Syst. Mol. Biol.* 4:109-115; Horton & Nakai (1997) *Intellig. Syst. Mol. Biol.* 5:147-152]; (ii) SignalP [Nielsen & Krogh (1998) in *Proceedings of the Sixth International Conference on Intelligent Systems for Molecular Biology* (*ISMB* 6), AAAI Press, Menlo Park, California, pp. 122-130; Nielsen *et al.* (1999) *Protein Engineering* 12:3-9; Nielsen *et al.* (1997). *Int. J. Neural Sys.* 8:581-599]; and (iii) visual inspection of the ORF sequences. Where a signal sequences is given a "possible site" value, the value represents the C-terminus residue of the signal peptide *e.g.* a "possible site" of 26 means that the signal sequence consists of amino acids 1-26.

Lipoprotein-specific signal peptides were located using three different approaches: (i) PSORT [see above]; (ii) the "prokaryotic membrane lipoprotein lipid attachment site" PROSITE motif [Hofmann *et al.* (1999) *Nucleic Acids Res.* 27:215-219; Bucher & Bairoch (1994) in *Proceedings 2nd International Conference on Intelligent Systems for Molecular Biology* (ISMB-94), AAAI Press, pages 53-61]; and (iii) the FINDPATTERNS program available in the GCG Wisconsin Package, using the pattern `(M,L,V)x{9,35}LxxCx`.

Transmembrane domains were located using two approaches: (i) PSORT [see above]; (ii) TopPred [von Heijne (1992) *J. Mol. Biol.* 225:487-494].

LPXTG motifs, characteristic of cell-wall attached proteins in Gram-positive bacteria [Fischetti *et al.* (1990) *Mol Microbiol* 4:1603-5] were located with FINDPATTERNS using the pattern `(L,I,V,M,Y,F)Px(T,A,S,G)(G,N,S,T,A,L)`.

RGD motifs, characteristic of cell-adhesion molecules [D'Souza *et al.* (1991) *Trends Biochem Sci* 16:246-50] were located using FINDPATTERNS.

Enzymes belonging to the glycolytic pathway were also selected as antigens, because these have been found experimentally expressed on the surface of *Streptococci* [*e.g.* Pancholi & Fischetti (1992) *J Exp Med* 176:415-26; Pancholi & Fischetti (1998) *J Biol Chem* 273:14503-15].

Cloning, expression and purification of proteins

GBS genes were cloned to facilitate expression in *E.coli* as two different types of fusion proteins:

a) proteins having a hexa-histidine tag at the amino-terminus (His-gbs)

b) proteins having a GST fusion partner at the amino-terminus (Gst-gbs)

Cloning was performed using the Gateway™ technology (Life Technologies), which is based on the site-specific recombination reactions that mediate integration and excision of phage lambda into and from the *E.coli* genome. A single cloning experiment included the following steps:

1- Amplification of GBS chromosomal DNA to obtain a PCR product coding for a single ORF flanked by *att*B recombination sites.

2- Insertion of the PCR product into a pDONR vector (containing *att*P sites) through a BP reaction (*att*B x *att*P sites). This reaction gives a so called 'pEntry' vector, which now contains *att*L sites flanking the insert.

3- Insertion of the GBS gene into *E.coli* expression vectors (pDestination vectors, containing *att*R sites) through a LR reaction between pEntry and pDestination plasmids (*att*L x *att*R sites).

A) Chromosomal DNA preparation

For chromosomal DNA preparation, GBS strain 2603 V/R (Istituto Superiore Sanità, Rome) was grown to exponential phase in 2 litres TH Broth (Difco) at 37°C, harvested by centrifugation, and dissolved in 40 ml TES (50 mM Tris pH 8, 5 mM EDTA pH 8, 20% sucrose). After addition of 2.5 ml lysozyme solution (25 mg/ml in TES) and 0.5 ml mutanolysin (Sigma M-9901, 25000U/ml in H_2O), the suspension was incubated at 37°C for 1 hour. 1 ml RNase (20 mg/ml) and 0.1 ml proteinase K (20 mg/ml) were added and incubation was continued for 30 min. at 37°C.

Cell lysis was obtained by adding 5 ml sarkosyl solution (10% N-laurylsarcosine in 250 mM EDTA pH 8.0), and incubating 1 hour at 37°C with frequent inversion. After sequential extraction with phenol, phenol-chloroform and chloroform, DNA was precipitated with 0.3M sodium acetate pH 5.2 and 2 volumes of absolute ethanol. The DNA pellet was rinsed with 70% ethanol and dissolved in TE buffer (10 mM Tris-HCl, 1 mM EDTA, pH 8). DNA concentration was evaluated by OD_{260}.

B) Oligonucleotide design

Synthetic oligonucleotide primers were designed on the basis of the coding sequence of each ORF. The aim was to express the protein's extracellular region. Accordingly, predicted signal peptides were omitted (by deducing the 5' end amplification primer sequence immediately downstream from the predicted leader sequence) and C-terminal cell-wall ancoring regions were removed (*e.g.* LPXTG motifs and downstream amino acids). Where additional nucleotides have been deleted, this is indicated by the suffix 'd' (*e.g.* 'GBS352d' – see Table V). Conversely, a suffix 'L' refers to expression without these deletions. Deletions of C- or N-terminal residues were also sometimes made, as indicated by a 'C' or 'N' suffix.

The amino acid sequences of the expressed GBS proteins (including 'd' and 'L' forms *etc.*) are definitively defined by the sequences of the oligonuclotide primers given in Table II.

5' tails of forward primers and 3' tails of reverse primers included *att*B1 and *att*B2 sites respectively:

Forward primers: 5'-GGGGACAAGTTTGTACAAAAAAGCAGGCTCT-ORF in frame-3' (the TCT sequence preceding the ORF was omitted when the ORF's first coding triplet began with T).

Reverse primers: 5'-GGGGACCACTTTGTACAAGAAAGCTGGGTT-ORF reverse complement-3'.

The number of nucleotides which hybridized to the sequence to be amplified depended on the melting temperature of the primers, which was determined as described by Breslauer *et al.* [*PNAS USA* (1986) 83:3746-50]. The average melting temperature of the selected oligos was 50-55°C for the hybridizing region and 80-85°C for the whole oligos.

C) Amplification

The standard PCR protocol was as follows: 50 ng genomic DNA were used as template in the presence of 0.5 μM each primer, 200 μM each dNTP, 1.5 mM $MgCl_2$, 1x buffer minus Mg^{++} (Gibco-BRL) and 2 units of Taq DNA polymerase (Platinum Taq, Gibco-BRL) in a final volume of 100 μl. Each sample underwent a double-step of amplification: 5 cycles performed using as the hybridizing temperature 50°C, followed by 25 cycles at 68°C.

The standard cycles were as follows:

	Denaturation: 94°C, 2 min
5 cycles:	Denaturation: 94°C, 30 seconds
	Hybridization: 50°C, 50 seconds
	Elongation: 72°C, 1 min. or 2 min. and 40 sec.
25 cycles :	Denaturation: 94°C, 30 seconds
	Hybridization: 68°C, 50 seconds

Elongation: 72°C, 1 min. or 2 min. and 40 sec.

Elongation time was 1 minute for ORFs shorter than 2000bp and 2:40 minutes for ORFs longer than 2000bp. Amplifications were performed using a Gene Amp PCR system 9600 (Perkin Elmer).

To check amplification results, 2µl of each PCR product were loaded onto 1-1.5 agarose gel and the size of amplified fragments was compared with DNA molecular weight standards (DNA marker IX Roche, 1kb DNA ladder Biolabs).

Single band PCR products were purified by PEG precipitation: 300 µl of TE buffer and 200 µl of 30% PEG 8000/30 mM $MgCl_2$ were added to 100 µl PCR reaction. After vortexing, the DNA was centrifuged for 20 min at 10000*g*, washed with 1 vol. 70% ethanol and the pellet dissolved in 30 µl TE. PCR products smaller than 350 bp were purified using a PCR purification Kit (Qiagen) and eluted with 30 µl of the provided elution buffer.

In order to evaluate the yield, 2µl of the purified DNA were subjected to agarose gel electrophoresis and compared to titrated molecular weight standards.

D) Cloning of PCR products into expression vectors

Cloning was performed following the Gateway™ technology's "one-tube protocol", which consists of a two step reaction (BP and LR) for direct insertion of PCR products into expression vectors.

BP reaction (*att*B x *att*P sites): The reaction allowed insertion of the PCR product into a pDONR vector. The pDONR™ 201 vector we used contains the killer toxin gene *ccdB* between *att*P1 and *att*P2 sites to minimize background colonies lacking the PCR insert, and a selectable marker gene for kanamycin resitance. The reaction resulted in a so called pEntry vector, in which the GBS gene was located between *att*L1 and *att*L2 sites.

60 fmol of PCR product and 100 ng of pDONR™ 201 vector were incubated with 2.5 µl of BP clonase™ in a final volume of 12.5 µl for 4 hours at 25°C.

LR reaction (*att*L x *att*R sites): The reaction allowed the insertion of the GBS gene, now present in the pEntry vector, into *E.coli* expression vectors (pDestination vectors, containing *att*R sites). Two pDestination vectors were used (pDEST15 for N- terminal GST fusions – Figure 86; and pDEST17-1 for N-terminal His-tagged fusions – Figure 87). Both allow transcription of the ORF fusion coding mRNA under T7 RNA polymerase promoter [Studier *et al* (1990) *Meth. Enzymol* 185: 60*ff*].

To 5 µl of BP reaction were added 0.25 µl of 0.75 M NaCl, 100 ng of destination vector and 1.5 µl of LR clonase™ . The reaction was incubated at 25°C for 2 hours and stopped with 1 µl of 1 mg/ml proteinase K solution at 37°C for 15 min.

1 µl of the completed reaction was used to transform 50 µl electrocompetent BL21-SI™ cells (0.1 cm, 200 ohms, 25 µF). BL21-SI cells contain an integrated T7 RNA polymerase gene under the control of the salt-inducible *prU* promoter [Gowrishankar (1985) *J. Bacteriol.* 164:434*ff*]. After electroporation cells were diluted in 1ml SOC medium (20 g/l bacto-tryptone, 5 g/l yeast extract, 0.58 g/l NaCl, 0.186 g/l KCl, 20 mM glucose, 10 mM $MgCl_2$) and incubated at 37°C for 1 hour. 200 µl cells were plated onto LBON plates (Luria Broth medium without NaCl) containing 100 µg/ ml ampicillin. Plates were then incubated for 16 hours at 37°C.

Entry clones: In order to allow the future preparation of Gateway compatible pEntry plasmids containing genes which might turn out of interest after immunological assays, 2.5 µl of BP reaction were incubated for 15 min in the presence of 3 µl 0.15 mg/ml proteinase K solution and then kept at –20°C. The reaction was in this way available to transform *E.coli* competent cells so as to produce Entry clones for future introduction of the genes in other Destination vectors.

E) Protein expression

Single colonies derived from the transformation of LR reactions were inoculated as small-scale cultures in 3 ml LBON 100 µg/ml ampicillin for overnight growth at 25°C. 50-200 µl of the culture was inoculated in 3 ml LBON/Amp to an initial OD600 of 0.1. The cultures were grown at 37°C until OD600 0.4-0.6 and recombinant protein expression was induced by adding NaCl to a final concentration of 0.3 M. After 2 hour incubation the final OD was checked and the cultures were cooled on ice. 0.5 OD_{600} of cells were harvested by centrifugation. The cell pellet was suspended in 50 µl of protein Loading Sample Buffer (50 mM TRIS-HCl pH 6.8, 0.5% w/v SDS, 2.5% v/v glycerin, 0.05% w/v Bromophenol Blue, 100 mM DTT) and incubated at 100 °C for 5 min. 10 µl of sample was analyzed by SDS-PAGE and Coomassie Blue staining to verify the presence of induced protein band.

F) Purification of the recombinant proteins

Single colonies were inoculated in 25 ml LBON 100 µg/ml ampicillin and grown at 25°C overnight. The overnight culture was inoculated in 500 ml LBON/amp and grown under shaking at 25 °C until OD_{600} values of 0.4-0.6. Protein expression was then induced by adding NaCl to a final concentration of 0.3 M. After 3 hours incubation at 25 °C the final OD_{600} was checked and the cultures were cooled on ice. After centrifugation at 6000 rpm (JA10 rotor, Beckman) for 20 min., the cell pellet was processed for purification or frozen at –20 °C.

Proteins were purified in 1 of 3 ways depending on the fusion partner and the protein's solubility:

Purification of soluble His-tagged proteins from *E.coli*

1. Transfer pellets from –20°C to ice bath and reconstitute each pellet with 10 ml B-PER™ solution (Bacterial-Protein Extraction Reagent, Pierce cat. 78266), 10 µl of a 100 mM $MgCl_2$ solution, 50

µl of DNAse I (Sigma D-4263, 100 Kunits in PBS) and 100 µl of 100 mg/ml lysozyme in PBS (Sigma L-7651, final concentration 1 mg/ml).

2. Transfer resuspended pellets in 50 ml centrifuge tubes and leave at room temperature for 30-40 minutes, vortexing 3-4 times.
3. Centrifuge 15-20 minutes at about 30-40000 x *g*.
4. Prepare Poly-Prep (Bio-Rad) columns containing 1 ml of Fast Flow Ni-activated Chelating Sepharose (Pharmacia). Equilibrate with 50 mM phosphate buffer, 300 mM NaCl, pH 8.0.
5. Store the pellet at –20°C, and load the supernatant on to the columns.
6. Discard the flow through.
7. Wash with 10 ml 20 mM imidazole buffer, 50 mM phosphate, 300 mM NaCl, pH 8.0.
8. Elute the proteins bound to the columns with 4.5 ml (1.5 ml + 1.5 ml + 1.5 ml) 250 mM imidazole buffer, 50 mM phosphate, 300 mM NaCl, pH 8.0 and collect three fractions of ~1.5 ml each. Add to each tube 15 µl DTT 200 mM (final concentration 2 mM).
9. Measure the protein concentration of the collected fractions with the Bradford method and analyse the proteins by SDS-PAGE.
10. Store the collected fractions at +4°C while waiting for the results of the SDS-PAGE analysis.
11. For immunisation prepare 4-5 aliquots of 20-100 µg each in 0.5 ml in 40% glycerol. The dilution buffer is the above elution buffer, plus 2 mM DTT. Store the aliquots at –20°C until immunisation.

Purification of His-tagged proteins from inclusion bodies

1. Bacteria are collected from 500 ml cultures by centrifugation. If required store bacterial pellets at -20°C. Transfer the pellets from -20°C to room temperature and reconstitute each pellet with 10 ml B-PER™ solution, 10 µl of a 100 mM $MgCl_2$ solution (final 1 mM), 50 µl of DNAse I equivalent to 100 Kunits units in PBS and 100 µl of a 100 mg/ml lysozime (Sigma L-7651) solution in PBS (equivalent to 10 mg, final concentration 1 mg/ml).
2. Transfer the resuspended pellets in 50 ml centrifuge tubes and let at room temperature for 30-40 minutes, vortexing 3-4 times.
3. Centrifuge 15 minutes at 30-4000 x g and collect the pellets.
4. Dissolve the pellets with 50 mM TRIS-HCl, 1 mM TCEP {Tris(2-carboxyethyl)-phosphine hydrochloride, Pierce} , 6M guanidine hydrochloride, pH 8.5. Stir for ~ 10 min. with a magnetic bar.
5. Centrifuge as described above, and collect the supernatant.
6. Prepare Poly-Prep (Bio-Rad) columns containing 1 ml of Fast Flow Ni-activated Chelating Sepharose (Pharmacia). Wash the columns twice with 5 ml of H_20 and equilibrate with 50 mM TRIS-HCl, 1 mM TCEP, 6M guanidine hydrochloride, pH 8.5.

7. Load the supernatants from step 5 onto the columns, and wash with 5 ml of 50 mM TRIS-HCl buffer, 1 mM TCEP, 6M urea, pH 8.5
8. Wash the columns with 10 ml of 20 mM imidazole, 50 mM TRIS-HCl , 6M urea, 1 mM TCEP, pH 8.5. Collect and set aside the first 5 ml for possible further controls.
9. Elute proteins bound to columns with 4.5ml buffer containing 250 mM imidazole, 50 mM TRIS-HCl, 6M urea, 1 mM TCEP, pH 8.5. Add the elution buffer in three 1.5 ml aliquots, and collect the corresponding three fractions. Add to each fraction 15 µl DTT (final concentration 2 mM).
10. Measure eluted protein concentration with Bradford method and analyse proteins by SDS-PAGE.
11. Dialyse overnight the selected fraction against 50 mM Na phosphate buffer, pH 8.8, containing 10% glycerol, 0.5 M arginine, 5 mM reduced glutathione, 0.5 mM oxidized glutathione, 2 M urea.
12. Dialyse against 50 mM Na phosphate buffer, pH 8.8, containing 10% glycerol, 0.5 M arginine, 5 mM reduced glutathione, 0.5 mM oxidized glutathione.
13. Clarify the dialysed protein preparation by centrifugation and discard the non-soluble material and measure the protein concentration with the Bradford method.
14. For each protein destined to the immunization prepare 4-5 aliquot of 20-100 µg each in 0.5 ml after having adjusted the glycerol content up to 40%. Store the prepared aliquots at –20° C until immunization.

Purification of GST-fusion proteins from *E.coli*

1. Bacteria are collected from 500 ml cultures by centrifugation. If required store bacterial pellets at -20°C. Transfer the pellets from –20°C to room temperature and reconstitute each pellet with 10 ml B-PER™ solution, 10 µl of a 100 mM $MgCl_2$ solution (final 1 mM), 50 µl of DNAse I equivalent to 100 Kunits units in PBS and 100 µl of a 100 mg/ml lysozime (Sigma L-7651) solution in PBS (equivalent to 10 mg, final concentration 1 mg/ml).
2. Transfer the resuspended pellets in 50 ml centrifuge tubes and let at room temperature for 30-40 minutes, vortexing 3-4 times.
3. Centrifuge 15-20 minutes at about 30-40000 x *g*.
4. Discard centrifugation pellets and load supernatants onto the chromatography columns, as follows.
5. Prepare Poly-Prep (Bio-Rad) columns containing 0.5 ml of Glutathione-Sepharose 4B resin. Wash the columns twice with 1 ml of H_20 and equilibrate with 10 ml PBS, pH 7.4.
6. Load supernatants on to the columns and discard the flow through.
7. Wash the columns with 10 ml PBS, pH 7.4.
8. Elute proteins bound to columns with 4.5 ml of 50 mM TRIS buffer, 10 mM reduced glutathione, pH 8.0, adding 1.5 ml + 1.5 ml + 1.5 ml and collecting the respective 3 fractions of ~1.5 ml each.

9. Measure protein concentration of the fractions with the Bradford method and analyse the proteins by SDS-PAGE.
10. Store the collected fractions at +4°C while waiting for the results of the SDS-PAGE analysis.
11. For each protein destined for immunisation prepare 4-5 aliquots of 20-100 µg each in 0.5 ml of 40% glycerol. The dilution buffer is 50 mM TRIS-HCl, 2 mM DTT, pH 8.0. Store the aliquots at –20°C until immunisation.

Figures 167 to 170 and 238 to 239

For the experiments shown in Figures 167 to 170, Figure 238 and lanes 2-6 of Figure 239, the GBS proteins were fused at the N-terminus to thioredoxin and at C-terminus to a poly-His tail. The plasmid used for cloning is pBAD-DEST49 (Invitrogen Gateway™ technology) and expression is under the control of an L(+)-Arabinose dependent promoter. For the production of these GBS antigens, bacteria are grown on RM medium (6g/l Na_2HPO_4, 3g/l KH_2PO_4, 0.5 g/l NaCl, 1 g/l NH_4Cl, pH7,4, 2% casaminoacids, 0.2 % glucose, 1 mM $MgCl_2$) containing 100 µg/ml ampicillin. After incubation at 37°C until cells reach OD_{600}=0.5, protein expression is induced by adding 0.2% (v/v) L(+)Arabinose for 3 hours.

Immunisations with GBS proteins

The purified proteins were used to immunise groups of four CD-1 mice intraperitoneally. 20 µg of each purified protein was injected in Freund's adjuvant at days 1, 21 & 35. Immune responses were monitored by using samples taken on day 0 & 49. Sera were analysed as pools of sera from each group of mice.

FACScan bacteria Binding Assay procedure.

GBS serotype V 2603 V/R strain was plated on TSA blood agar plates and incubated overnight at 37°C. Bacterial colonies were collected from the plates using a sterile dracon swab and inoculated into 100ml Todd Hewitt Broth. Bacterial growth was monitored every 30 minutes by following OD_{600}. Bacteria were grown until OD_{600} = 0.7-0.8. The culture was centrifuged for 20 minutes at 5000rpm. The supernatant was discarded and bacteria were washed once with PBS, resuspended in ½ culture volume of PBS containing 0.05% paraformaldehyde, and incubated for 1 hour at 37°C and then overnight at 4°C.

50µl bacterial cells (OD_{600} 0.1) were washed once with PBS and resuspended in 20µl blocking serum (Newborn Calf Serum, Sigma) and incubated for 20 minutes at room temperature. The cells were then incubated with 100µl diluted sera (1:200) in dilution buffer (20% Newborn Calf Serum 0.1% BSA in PBS) for 1 hour at 4°C. Cells were centrifuged at 5000rpm, the supernatant aspirated and cells washed by adding 200µl washing buffer (0.1% BSA in PBS). 50µl R-Phicoerytrin conjugated $F(ab)_2$ goat anti-mouse, diluted 1:100 in dilution buffer, was added to each sample and incubated for 1 hour at 4°C. Cells were spun down by centrifugation at 5000rpm and washed by adding 200µl of washing buffer. The

supernatant was aspirated and cells resuspended in 200µl PBS. Samples were transferred to FACScan tubes and read. The condition for FACScan setting were: FL2 on; FSC-H threshold:54; FSC PMT Voltage: E 02; SSC PMT: 516; Amp. Gains 2.63; FL-2 PMT: 728. Compensation values: 0.

Samples were considered as positive if they had a Δ mean values > 50 channel values.

Whole Extracts preparation

GBS serotype III COH1 strain and serotype V 2603 V/R strain cells were grown overnight in Todd Hewitt Broth. 1ml of the culture was inoculated into 100ml Todd Hewitt Broth. Bacterial growth was monitored every 30 minutes by following OD_{600}. The bacteria were grown until the OD reached 0.7-0.8. The culture was centrifuged for 20 minutes at 5000 rpm. The supernatant was discarded and bacteria were washed once with PBS, resuspended in 2ml 50mM Tris-HCl, pH 6.8 adding 400 units of Mutanolysin (Sigma-Aldrich) and incubated 3 hrs at 37°C. After 3 cycles of freeze/thaw, cellular debris were removed by centrifugation at 14000*g* for 15 minutes and the protein concentration of the supernatant was measured by the Bio-Rad Protein assay, using BSA as a standard.

Western blotting

Purified proteins (50ng) and total cell extracts (25µg) derived from GBS serotype III COH1 strain and serotype V 2603 V/R strain were loaded on 12% or 15% SDS-PAGE and transferred to a nitrocellulose membrane. The transfer was performed for 1 hours at 100V at 4°C, in transferring buffer (25mM Tris base, 192mM glycine, 20% methanol). The membrane was saturated by overnight incubation at 4°C in saturation buffer (5 % skimmed milk, 0.1% Tween 20 in PBS). The membrane was incubated for 1 hour at room temperature with 1:1000 mouse sera diluted in saturation buffer. The membrane was washed twice with washing buffer (3 % skimmed milk, 0.1% Tween 20 in PBS) and incubated for 1 hour with a 1:5000 dilution of horseradish peroxidase labelled anti-mouse Ig (Bio-Rad). The membrane was washed twice with 0.1% Tween 20 in PBS and developed with the Opti-4CN Substrate Kit (Bio-Rad). The reaction was stopped by adding water.

Unless otherwise indicated, lanes 1, 2 and 3 of blots in the drawings are: (1) the purified protein; (2) GBS-III extracts; and (3) GBS-V extracts. Molecular weight markers are also shown.

In vivo *passive protection assay in neonatal sepsis mouse model.*

The immune sera collected from the CD1 immunized mice were tested in a mouse neonatal sepsis model to verify their protective efficacy in mice challenged with GBS serotype III. Newborn Balb/C littermates were randomly divided in two groups within 24 hrs from birth and injected subcutaneously with 25µl of diluted sera (1:15) from immunized CD1 adult mice. One group received preimmune sera, the other received immune sera. Four hours later all pups were challenged with a 75% lethal dose of the GBS serotype III COH1 strain. The challenge dose obtained diluting a mid log phase culture was administered subcutaneously in 25 µl of saline. The number of pups surviving GBS infection was assessed every 12 hours for 4 days. Results are in Table III.

Example 1

A DNA sequence (GBSx1402) was identified in *S.agalactiae* <SEQ ID 1> which encodes the amino acid sequence <SEQ ID 2>. Analysis of this protein sequence reveals the following:

```
Possible site: 27
>>> Seems to have an uncleavable N-term signal seq
   INTEGRAL    Likelihood = -0.48   Transmembrane  169 - 185 ( 169 - 185)

----- Final Results -----
               bacterial membrane --- Certainty=0.1192(Affirmative) < succ>
                bacterial outside --- Certainty=0.0000(Not Clear) < succ>
              bacterial cytoplasm --- Certainty=0.0000(Not Clear) < succ>
```

The protein has homology with the following sequences in the GENPEPT database.

```
>GP:CAB88235 GB:AL353012 hypothetical serine-rich repeat protein
          [Schizosaccharomyces pombe]
 Identities = 41/152 (26%), Positives = 75/152 (48%), Gaps = 4/152 (2%)

Query: 22  SSIGYADTSDKNTDTSVVTTTLSEEKRSDELDQSSTGSSSENESSSSSEPETNPSTNPPT 81
           SS   +++S +++D+S  ++    E  S+  D SS+ SSSE+ESSS     ++ S++  +
Sbjct: 132 SSDSESESSSEDSDSSSSSSDSESESSSEGSDSSSSSSSSESESSSEDNDSSSSSSDSES 191

Query: 82  TEPSQPSPSEENKPDGRTKTE---IGNNKDISSGTKVLISEDSIKNFSKASSDQEEVDRD 138
              S+ S S  +  D  +++      ++   SS      SED+  + S + S+ E    D
Sbjct: 192 ESSSEDSDSSSSSSDSESESSSEGSDSSSSSSSESESSSEDNDSSSSSSDSESESSSED 251

Query: 139 ESSSSKANDGK-KGHSKPKKELPKTGDSHSDT 169
             SSS ++D + +  SK       + DS  D+
Sbjct: 252 SDSSSSSSDSESESSSKDSDSSSNSSDSEDDS 283
```

There is also homology to SEQ ID 1984.

A related GBS gene <SEQ ID 8785> and protein <SEQ ID 8786> were also identified. Analysis of this protein sequence reveals the following:

```
Lipop: Possible site: -1   Crend: 5
McG: Discrim Score:      6.72
GvH: Signal Score (-7.5): -4.34
     Possible site: 27
>>> Seems to have an uncleavable N-term signal seq
ALOM program   count: 1 value:  -0.48 threshold:  0.0
   INTEGRAL    Likelihood = -0.48   Transmembrane  169 - 185 ( 169 - 185)
   PERIPHERAL  Likelihood =  0.16       7
 modified ALOM score:   0.60

*** Reasoning Step: 3

----- Final Results -----
               bacterial membrane --- Certainty=0.1192(Affirmative) < succ>
                bacterial outside --- Certainty=0.0000(Not Clear) < succ>
              bacterial cytoplasm --- Certainty=0.0000(Not Clear) < succ>

LPXTG motif: 159-163
```

SEQ ID 2 (GBS4) was expressed in *E.coli* as a GST-fusion product. SDS-PAGE analysis of total cell extract is shown in Figure 9 (lane 3; MW 43.1kDa) and Figure 63 (lane 4; MW 50kDa). It was also expressed in *E.coli* as a His-fusion product. SDS-PAGE analysis of total cell extract is shown in Figure 12 (lane 7; MW 30kDa), Figure 63 (lane 3; MW 30kDa) and in Figure 178 (lane 3; MW 30kDa).

GBS4-GST was purified as shown in Figure 190 (lane 6) and Figure 209 (lane 8).

```
Query: 1   MITQEMKEIINSQLAMVATVDAKGQPNIGPKRSMRLWDDKTFIYNENTDGQTRINIEDNG 60
           M+T EM + I  +L  VAT D +G PN+ P     R  D++T +  +N   +T  N+ +N
Sbjct: 1   MMTPEMMDAIEKELVFVATADEEGTPNVVPIGFARPLDERTILIADNYMKKTIRNLHENP 60

Query: 61  KIEIAFVDRERLLGYRFVGTAEIQTEGTYYEAAKKWAEGRMG--VPKAVGIIHVERIFNL 118
           +I +      R   Y+F GT EI   G Y++   +WA+  M    PK+  ++ VE I+++
Sbjct: 61  RIAL-IPQNARECPYQFKGTVEIFKSGKYFDMVVEWAQNVMTELEPKSAILMTVEEIYSV 119

Query: 119 QSGANAGKEI 128
           + G  AG+++
Sbjct: 120 KPGPEAGEKV 129
```

A related DNA sequence was identified in *S.pyogenes* <SEQ ID 797> which encodes the amino acid sequence <SEQ ID 798>. Analysis of this protein sequence reveals the following:

```
Possible site: 24
>>> Seems to have no N-terminal signal sequence

----- Final Results -----
            bacterial cytoplasm --- Certainty=0.0789(Affirmative) < succ>
             bacterial membrane --- Certainty=0.0000(Not Clear) < succ>
              bacterial outside --- Certainty=0.0000(Not Clear) < succ>
```

An alignment of the GAS and GBS proteins is shown below:

```
 Identities = 123/128 (96%), Positives = 127/128 (99%)

Query: 1   MITQEMKEIINSQLAMVATVDAKGQPNIGPKRSMRLWDDKTFIYNENTDGQTRINIEDNG 60
           MITQEMK++IN+QLAMVATVDAKGQPNIGPKRSMRLWDDKTFIYNENTDGQTRINIEDNG
Sbjct: 1   MITQEMKDLINNQLAMVATVDAKGQPNIGPKRSMRLWDDKTFIYNENTDGQTRINIEDNG 60

Query: 61  KIEIAFVDRERLLGYRFVGTAEIQTEGTYYEAAKKWAEGRMGVPKAVGIIHVERIFNLQS 120
           KIEIAFVDRERLLGYRFVGTAEIQTEG YYEAAKKWA+GRMGVPKAVGIIHVERIFNLQS
Sbjct: 61  KIEIAFVDRERLLGYRFVGTAEIQTEGAYYEAAKKWAQGRMGVPKAVGIIHVERIFNLQS 120

Query: 121 GANAGKEI 128
           GANAGKEI
Sbjct: 121 GANAGKEI 128
```

Based on this analysis, it was predicted that these proteins and their epitopes could be useful antigens for vaccines or diagnostics.

Example 253

A DNA sequence (GBSx0268) was identified in *S.agalactiae* <SEQ ID 799> which encodes the amino acid sequence <SEQ ID 800>. Analysis of this protein sequence reveals the following:

```
Possible site: 22
>>> Seems to have a cleavable N-term signal seq.
   INTEGRAL    Likelihood = -5.47   Transmembrane 1028 -1044 (1027 -1048)

----- Final Results -----
              bacterial membrane --- Certainty=0.3187(Affirmative) < succ>
               bacterial outside --- Certainty=0.0000(Not Clear) < succ>
             bacterial cytoplasm --- Certainty=0.0000(Not Clear) < succ>
```

The protein has homology with the following sequences in the GENPEPT database:

```
!GB:AF054892 surface antigen BspA [Bacteroides forsy...
!GB:AF054892 surface antigen BspA [Bacteroides forsy...
!GB:AF054892 surface antigen BspA [Bacteroides forsy...
!GB:AF054892 surface antigen BspA [Bacteroides forsy...
!GB:AF054892 surface antigen BspA [Bacteroides forsy...

>GP:AAC82625 GB:AF054892 surface antigen BspA [Bacteroides
```

```
          forsythus]
 Identities = 143/566 (25%), Positives = 243/566 (42%), Gaps = 52/566 (9%)

Query: 95  VPKAKPEVTQEASNSSNDASKVEVPKQDTASKKETLETSTWEAKDFVTRGDTLVG----F 150
           +P +   + + A    +    + +P   TA  +  L   T      +    T +G    F
Sbjct: 120 IPNSVTTIGEWAFKGCSGLKSITLPNSLTAIGQSALSGCTGLTSITIPNSVTTIGEWAFF 179

Query: 151 SKSGINKLSQTSHLVLPSHAA--DGTQLTQVASFAFTPDKKTAIAEYTSRLGENGKPSRL 208
             SG+  ++  + L     +A      LT +      PD  T I E   + G +G  S
Sbjct: 180 GCSGLTSITFPNSLTAIGESAFYGCGALTSIT----LPDALTTIGESAFK-GCSGLKSIT 234

Query: 209 DIDQKEIIDEGEIFNAYQLTKLTIPNGYKSIGQDAFVDNKNIAEVNLPESLETISDYAFA 268
             +    I E   ++    LT +T+P+   +IG+ AF     +  +  P SL TI + AF
Sbjct: 235 FPNSLTTIGESAFYDCGALTSITLPDALTTIGRSAFYGCSGLKSITFPNSLTTIGESAFY 294

Query: 269 HM-SLKQVKLPDNLKVIGELAFFDNQIGGKLYLPRHLIKLAERAFKSNRIQTVEFLGSKL 327
           +  SL  + +P+++  IG  AF+       + LP  L  + ERAF +  + T   + + +
Sbjct: 295 NCGSLTSITIPNSVTTIGRSAFYGCSGLKSITLPDGLTTIEERAFYNCGVLTSITIPNSV 354

Query: 328 KVIGEASFQD-NNLRNVMLPDGLEKIESEAFTGNPGDEHYNNQVVLRTRTGQNPHQLATE 386
             IGE++F    + L+++ LPDGL  IE  AF          N   L + T  N      E
Sbjct: 355 ATIGESAFYGCSGLKSITLPDGLTTIEWGAFY---------NCGALTSITIPNSVSTIGE 405

Query: 387 NTYVNPDKSLWRATPDMDYTKWLEEDFTYQKNSVTGFS---NKGLQKVRRNKNLEIPKQH 443
           + +      +L   T   D    ++ D  +++ +++G       G + V   K  ++ K+
Sbjct: 406 SAFYGCG-ALKDVTVAWDTPIDIQRD-VFRELTLSGIRLHVPAGKKTVYEAK--DVWKEF 461

Query: 444 NGITITEIGDNAFRNVDFQSKTLRKYDLEEIKLPSTIRKIGAFAFQSNNLKSFEASEDLE 503
           N +   + G   + N D  +KTL   +      P T + +  FA  ++ L
Sbjct: 462 NIVEDDDFGGLQW-NYDAATKTLTITN----PTPDTPKPMPNFATPNDQLW--------- 507

Query: 504 EIKEGAFMNNRIGTLDLKDKLIKIGDAAFH-INHIYAIVLPESVQEIGRSAFRQNGALHL 562
              GAF    I  + + D +  +GD AF   + + +I LP+SV  IG+SAF     L
Sbjct: 508 ----GAFQKE-IQKITIGDGVTSVGDFAFSGCDALKSITLPKSVTTIGQSAFSGCWDLRS 562

Query: 563 MFIGNKVKTIGEMAFLSNKLESVNLSEQKQLKTIEVQAFS-DNALSEVVLPPNLQTIREE 621
           + + + V TIGE AF  + LE  +++   K +  I  + F     +L+ + LP  L  I ++
Sbjct: 563 LTLPDGVNTIGEKAFY-DCLELTSITIPKSVTAIGQETFHYCVSLTSLTLPDALTAIGKK 621

Query: 622 AF-KRNHLKEVKGSSTLSQITFNAFD 646
           AF   N L  V    +++ I  NAFD
Sbjct: 622 AFYSCNALTSVTFPKSITTIGENAFD 647
 Identities = 109/407 (26%), Positives = 175/407 (42%), Gaps = 48/407 (11%)

Query: 222 FNAYQLTKLTIPNGYKSIGQDAFVDNKNIAEVNLPESLETISDYAFAHMS-LKQVKLPDN 280
           F+   LT +T+PN   +IG  AF     +  + +P S+ TI  ++AF   S LK + LP++
Sbjct: 87  FSDCALTSVTLPNSLTAIGDHAFKGCSGLTSITIPNSVTTIGEWAFKGCSGLKSITLPNS 146

Query: 281 LKVIGELAFFDNQIGGKLYLPRHLIKLAERAFKSNRIQTVEFLGSKLKVIGEASFQD-NN 339
           L  IG+ A          + +P  +  + E AF      T     + L  IGE++F
Sbjct: 147 LTAIGQSALSGCTGLTSITIPNSVTTIGEWAFFGCSGLTSITFPNSLTAIGESAFYGCGA 206

Query: 340 LRNVMLPDGLEKIESEAFTGNPGDEHYNNQVVLRTRTGQNPHQLATENTYVNPDKSLWRA 399
           L ++ LPD L  I   AF G  G         L++ T  N      E+ + +
Sbjct: 207 LTSITLPDALTTIGESAFKGCSG---------LKSITFPNSLTTIGESAFYDCGALTSIT 257

Query: 400 TPDMDYTKWLEEDFTYQKNSVTGFSNKGLQKVRRNKNLEIPKQHNGITITEIGDNAFRNV 459
            PD                ++T             K++  P       ++T IG++AF N
Sbjct: 258 LPD----------------ALTTIGRSAFYGCSGLKSITFPN-----SLTTIGESAFYNC 296

Query: 460 DFQSKTLRKYDLEEIKLPSTIRKIGAFAFQS-NNLKSFEASEDLEEIKEGAFMNNRIGT- 517
                   L  I +P+++  IG  AF   + LKS     + L  I+E AF N  + T
Sbjct: 297 G---------SLTSITIPNSVTTIGRSAFYGCSGLKSITLPDGLTTIEERAFYNCGVLTS 347

Query: 518 LDLKDKLIKIGDAAFH-INHIYAIVLPESVQEIGRSAFRQNGALHLMFIGNKVKTIGEMA 576
           + + + +  IG++AF+  + + +I LP+ +  I   AF   GAL  + I N V TIGE A
Sbjct: 348 ITIPNSVATIGESAFYGCSGLKSITLPDGLTTIEWGAFYNCGALTSITIPNSVSTIGESA 407
```

```
Query: 577 FLS-NKLESVNLSEQKQLKTIEVQAFSDNALSEVVL--PPNLQTIRE 620
           F     L+ V ++    +  I+   F +  LS + L  P   +T+ E
Sbjct: 408 FYGCGALKDVTVAWDTPI-DIQRDVFRELTLSGIRLHVPAGKKTVYE 453
 Identities = 111/465 (23%), Positives = 185/465 (38%), Gaps = 56/465 (12%)

Query: 141 VTRGDTLVGFSKSGINKLSQTSHLVLPSHAADGTQLTQVASFAF----------TPDKKT 190
           +T  D L    +S     S    +  P+       LT +   AF           PD  T
Sbjct: 210 ITLPDALTTIGESAFKGCSGLKSITFPN------SLTTIGESAFYDCGALTSITLPDALT 263

Query: 191 AIAEYTSRLGENGKPSRLDIDQKEIIDEGEIFNAYQLTKLTIPNGYKSIGQDAFVDNKNI 250
            I   ++  G +G  S     +    I E   +N   LT +TIPN   +IG+ AF     +
Sbjct: 264 TIGR-SAFYGCSGLKSITFPNSLTTIGESAFYNCGSLTSITIPNSVTTIGRSAFYGCSGL 322

Query: 251 AEVNLPESLETISDYAFAHMS-LKQVKLPDNLKVIGELAFFDNQIGGKLYLPRHLIKLAE 309
              + LP+ L TI + AF +   L  + +P+++  IGE AF+       + LP  L  +
Sbjct: 323 KSITLPDGLTTIEERAFYNCGVLTSITIPNSVATIGESAFYGCSGLKSITLPDGLTTIEW 382

Query: 310 RAFKSNRIQTVEFLGSKLKVIGEASFQD-NNLRNVMLP-DGLEKIESEAF-----TGNPG 362
            AF +    T   + + +  IGE++F      L++V + D    I+ + F     +G
Sbjct: 383 GAFYNCGALTSITIPNSVSTIGESAFYGCGALKDVTVAWDTPIDIQRDVFRELTLSGIRL 442

Query: 363 DEHYNNQVVLRTRTGQNPHQLATEN-------TYVNPDKSLWRATPDMDYTKWLEEDFTY 415
                + V   +       +  ++        Y    K+L     P  D  K +   +F
Sbjct: 443 HVPAGKKTVYEAKDVWKEFNIVEDDDFGGLQWNYDAATKTLTIINPTPDTPKPM-PNFAT 501

Query: 416 QKNSVTGFSNKGLQKVRRNKNLEIPKQHNGITITEIGDNAFRNVDFQSKTLRKYDLEEIK 475
             + + G   K +QK+             G  +T +GD AF   D          L+ I
Sbjct: 502 PNDQLWGAFQKEIQKIT-----------IGDGVTSVGDFAFSGCD---------ALKSIT 541

Query: 476 LPSTIRKIGAFAFQSN-NLKSFEASEDLEEIKEGAFMN-NRIGTLDLKDKLIKIGDAAFH 533
           LP ++  IG  AF    +L+S    + +  I E AF +   + ++ +   + IG   FH
Sbjct: 542 LPKSVTTIGQSAFSGCWDLRSLTLPDGVNTIGEKAFYDCLELTSITIPKSVTAIGQETFH 601

Query: 534 -INHIYAIVLPESVQEIGRSAFRQNGALHLMFIGNKVKTIGEMAF 577
              + ++ LP+++  IG+ AF    AL  +     + TIGE AF
Sbjct: 602 YCVSLTSLTLPDALTAIGKKAFYSCNALTSVTFPKSITTIGENAF 646
 Identities = 98/351 (27%), Positives = 152/351 (42%), Gaps = 53/351 (15%)

Query: 315 NRIQTVEFLGSKLKVIGEASFQDNNLRNVMLPDGLEKIESEAFTGNPGDEHYNNQVVLRT 374
           ++IQTV  +G  +  +G  +F D   L +V LP+ L  I   AF G  G          L +
Sbjct: 68  SKIQTVT-IGDGVTSVGNNAFSDCALTSVTLPNSLTAIGDHAFKGCSG---------LTS 117

Query: 375 RTGQNPHQLATENTYVNPDKSLWRATPDMDYTKWLEEDFTYQKNSVTGFSNKGLQKVRRN 434
            T   P+ + T   +     S  ++                    NS+T      L
Sbjct: 118 IT--IPNSVTTIGEWAFKGCSGLKSIT--------------LPNSLTAIGQSALSGCTGL 161

Query: 435 KNLEIPKQHNGITITEIGDNAF------RNVDFQSKTLRKYD--------LEEIKLPSTI 480
            ++ IP      ++T IG+ AF       ++ F +      +         L  I LP  +
Sbjct: 162 TSITIPN-----SVTTIGEWAFFGCSGLTSITFPNSLTAIGESAFYGCGALTSITLPDAL 216

Query: 481 RKIGAFAFQS-NNLKSFEASEDLEEIKEGAFMN-NRIGTLDLKDKLIKIGDAAFH-INHI 537
             IG  AF+  + LKS      L  I E AF +   + ++ L D L  IG  +AF+  + +
Sbjct: 217 TTIGESAFKGCSGLKSITFPNSLTTIGESAFYDCGALTSITLPDALTTIGRSAFYGCSGL 276

Query: 538 YAIVLPESVQEIGRSAFRQNGALHLMFIGNKVKTIGEMAFLS-NKLESVNLSEQKQLKTI 596
           +I  P S+  IG SAF   G+L  + I N V TIG  AF   + L+S+ L +   L TI
Sbjct: 277 KSITFPNSLTTIGESAFYNCGSLTSITIPNSVTTIGRSAFYGCSGLKSITLPD--GLTTI 334

Query: 597 EVQAFSD-NALSEVVLPPNLQTIREEAFKR-NHLKEVKGSSTLSQITFNAF 645
           E +AF +   L+ + +P ++ TI E AF   + LK +     L  I + AF
Sbjct: 335 EWGAFYNCGALTSITIPNSVATIGESAFYGCSGLKSITLPDGLTTIEWGAF 385
 Identities = 78/282 (27%), Positives = 123/282 (42%), Gaps = 46/282 (16%)

Query: 111 NDASKVEVPKQDTASKKETLETSTWEAKDFVTRGDTLVGFSKSGINKLSQTSHLVLPS-- 168
           N+AS  E+P     SK +T          VT GD +     +  + TS + LP+
Sbjct: 56  NNAS--EIPWHSLQSKIQT----------VTIGDGVTSVGNNAFSDCALTS-VTLPNSL 101

Query: 169 -----HAADG----------TQLTQVASFAFT----------PDKKTAIAEYTSRLGENG 203
```

```
                HA  G            +T +  +AF           P+  TAI + ++  G  G
Sbjct: 102 TAIGDHAFKGCSGLTSITIPNSVTTIGEWAFKGCSGLKSITLPNSLTAIGQ-SALSGCTG 160

Query: 204 KPSRLDIDQKEIIDEGEIFNAYQLTKLTIPNGYKSIGQDAFVDNKNIAEVNLPESLETIS 263
             S    +    I E   F    LT +T PN   +IG+ AF     +  + LP++L TI
Sbjct: 161 LTSITIPNSVTTIGEWAFFGCSGLTSITFPNSLTAIGESAFYGCGALTSITLPDALTTIG 220

Query: 264 DYAFAHMS-LKQVKLPDNLKVIGELAFFDNQIGGKLYLPRHLIKLAERAFKS-NRIQTVE 321
           + AF   S LK +  P++L  IGE AF+D      + LP  L  +   AF   + ++++
Sbjct: 221 ESAFKGCSGLKSITFPNSLTTIGESAFYDCGALTSITLPDALTTIGRSAFYGCSGLKSIT 280

Query: 322 FLGSKLKVIGEASFQD-NNLRNVMLPDGLEKIESEAFTGNPG 362
           F  S L  IGE++F +  +L ++ +P+ +  I   AF G  G
Sbjct: 281 FPNS-LTTIGESAFYNCGSLTSITIPNSVTTIGRSAFYGCSG 321
 Identities = 43/144 (29%), Positives = 70/144 (47%), Gaps = 4/144 (2%)

Query: 220 EIFNAYQ--LTKLTIPNGYKSIGQDAFVDNKNIAEVNLPESLETISDYAFAHM-SLKQVK 276
           +++ A+Q  + K+TI +G  S+G  AF     +  + LP+S+ TI   AF+    L+ +
Sbjct: 505 QLWGAFQKEIQKITIGDGVTSVGDFAFSGCDALKSITLPKSVTTIGQSAFSGCWDLRSLT 564

Query: 277 LPDNLKVIGELAFFDNQIGGKLYLPRHLIKLAERAFKSNRIQTVEFLGSKLKVIGEASFQ 336
           LPD +  IGE AF+D      + +P+ +  + +  F      T   L   L  IG+ +F
Sbjct: 565 LPDGVNTIGEKAFYDCLELTSITIPKSVTAIGQETFHYCVSLTSLTLPDALTAIGKKAFY 624

Query: 337 D-NNLRNVMLPDGLEKIESEAFTG 359
            N L +V  P  +  I   AF G
Sbjct: 625 SCNALTSVTFPKSITTIGENAFDG 648
 Identities = 43/134 (32%), Positives = 66/134 (49%), Gaps = 12/134 (8%)

Query: 511 MNNRIGTLDLKDKLIKIGDAAFHINHIYAIVLPESVQEIGRSAFRQNGALHLMFIGNKVK 570
           + ++I T+ + D +  +G+ AF    + ++ LP S+  IG  AF+    L  + I N V
Sbjct: 66  LQSKIQTVTIGDGVTSVGNNAFSDCALTSVTLPNSLTAIGDHAFKGCSGLTSITIPNSVT 125

Query: 571 TIGEMAFLS-NKLESVNLSEQKQLKTIEVQAFSD-NALSEVVLPPNLQTIREEAFKRNHL 628
           TIGE AF   + L+S+ L     L  I   A S    L+ + +P ++ TI E AF
Sbjct: 126 TIGEWAFKGCSGLKSITL--PNSLTAIGQSALSGCTGLTSITIPNSVTTIGEWAF----- 178

Query: 629 KEVKGSSTLSQITF 642
               G S L+ ITF
Sbjct: 179 ---FGCSGLTSITF 189
```

A related DNA sequence was identified in *S.pyogenes* <SEQ ID 801> which encodes the amino acid sequence <SEQ ID 802>. Analysis of this protein sequence reveals the following:

```
     Possible site: 21
>>> Seems to have a cleavable N-term signal seq.
   INTEGRAL    Likelihood = -2.44   Transmembrane  984 -1000 ( 984 -1001)

----- Final Results -----
               bacterial membrane --- Certainty=0.1977(Affirmative) < succ>
                bacterial outside --- Certainty=0.0000(Not Clear) < succ>
              bacterial cytoplasm --- Certainty=0.0000(Not Clear) < succ>

LPXTG motif: 975-979
```

An alignment of the GAS and GBS proteins is shown below:

```
 Identities = 751/1050 (71%), Positives = 861/1050 (81%), Gaps = 45/1050 (4%)

Query: 3    KKHLKTLALALTTVSVVTYSQEVYGLEREESVKQEQTQSA-SEDDWFEEDNERKTNVSKE 61
             KKHLKT+AL LTTVSVVT++QEV+ L +E  +KQ Q  S+ S  D+ E   + K  +++
Sbjct: 2    KKHLKTVALTLTTVSVVTHNQEVFSLVKEPILKQTQASSSISGADYAESSGKSKLKINET 61

Query: 62   NSTVDETVSDLFSDGNSNNSSSKTESVVSDPKQVPKAKPEVTQEASNSSNDASKVEVPKQ 121
             +  VD+TV+DLFSD  +     K         +Q  KA  E T E+        S++E  K+
Sbjct: 62   SGPVDDTVTDLFSDKRTTPEKIKDNLAKGPREQELKAVTENT-ESEKQITSGSQLEQSKE 120
```

```
Query: 122  DTASKKETLETSTWEAKDFVTRGDTLVGFSKSGINKLSQTSHLVLPSHAADGTQLTQVAS 181
              +  K     TS WE  DF+T+G+TLVG SKSG+ KLSQT HLVLPS AADGTQL QVAS
Sbjct: 121  SLSLNKTVPSTSNWEICDFITKGNTLVGLSKSGVEKLSQTDHLVLPSQAADGTQLIQVAS 180

Query: 182  FAFTPDKKTAIAEYTSRLGENGKPSRLDIDQKEIIDEGEIFNAYQLTKLTIPNGYKSIGQ 241
            FAFTPDKKTAIAEYTSR GENG+ S+LD+D KEII+EGE+FN+Y L K+TIP GYK IGQ
Sbjct: 181  FAFTPDKKTAIAEYTSRAGENGEISQLDVDGKEIINEGEVFNSYLLKKVTIPTGYKHIGQ 240

Query: 242  DAFVDNKNIAEVNLPESLETISDYAFAHMSLKQVKLPDNLKVIGELAFFDNQIGGKLYLP 301
            DAFVDNKNIAEVNLPESLETISDYAFAH++LKQ+ LPDNLK IGELAFFDNQI GKL LP
Sbjct: 241  DAFVDNKNIAEVNLPESLETISDYAFAHLALKQIDLPDNLKAIGELAFFDNQITGKLSLP 300

Query: 302  RHLIKLAERAFKSNRIQTVEFLGSKLKVIGEASFQDNNLRNVMLPDGLEKIESEAFTGNP 361
            R L++LAERAFKSN I+T+EF G+ LKVIGEASFQDN+L  +MLPDGLEKIESEAFTGNP
Sbjct: 301  RQLMRLAERAFKSNHIKTIEFRGNSLKVIGEASFQDNDLSQLMLPDGLEKIESEAFTGNP 360

Query: 362  GDEHYNNQVVLRTRTGQNPHQLATENTYVNPDKSLWRATPDMDYTKWLEEDFTYQKNSVT 421
            GD+HYNN+VVL T++G+NP  LATENTYVNPDKSLW+ +P++DYTKWLEEDFTYQKNSVT
Sbjct: 361  GDDHYNNRVVLWTKSGKNPSGLATENTYVNPDKSLWQESPEIDYTKWLEEDFTYQKNSVT 420

Query: 422  GFSNKGLQKVRRNKNLEIPKQHNGITITEIGDNAFRNVDFQSKTLRKYDLEEIKLPSTIR 481
            GFSNKGLQKV+RNKNLEIPKQHNG+TITEIGDNAFRNVDFQ+KTLRKYDLEE+KLPSTIR
Sbjct: 421  GFSNKGLQKVKRNKNLEIPKQHNGVTITEIGDNAFRNVDFQNKTLRKYDLEEVKLPSTIR 480

Query: 482  KIGAFAFQSNNLKSFEASEDLEEIKEGAFMNNRIGTLDLKDKLIKIGDAAFHINHIYAIV 541
            KIGAFAFQSNNLKSFEAS+DLEEIKEGAFMNNRI TL+LKDKL+ IGDAAFHINHIYAIV
Sbjct: 481  KIGAFAFQSNNLKSFEASDDLEEIKEGAFMNNRIETLELKDKLVTIGDAAFHINHIYAIV 540

Query: 542  LPESVQEIGRSAFRQNGALHLMFIGNKVKTIGEMAFLSNKLESVNLSEQKQLKTIEVQAF 601
            LPESVQEIGRSAFRQNGA +L+F+G+KVKT+GEMAFLSN+LE ++LSEQKQL  I VQAF
Sbjct: 541  LPESVQEIGRSAFRQNGANNLIFMGSKVKTLGEMAFLSNRLEHLDLSEQKQLTEIPVQAF 600

Query: 602  SDNALSEVVLPPNLQTIREEAFKRNHLKEVKGSSTLSQITFNAFDQNDGDKRFGKKVVVR 661
            SDNAL EV+LP +L+TIREEAFK+NHLK+++ +S LS I FNA D NDGD++F  KVVV+
Sbjct: 601  SDNALKEVLLPASLKTIREEAFKKNHLKQLEVASALSHIAFNALDDNDGDEQFDNKVVVK 660

Query: 662  THNNSHMLADGERFIIDPDKLSSTMVDLEKVLKIIEGLDYSTLRQTTQTQFREMTTAGKA 721
            TH+NS+ LADGE FI+DPDKLSST+VDLEK+LK+IEGLDYSTLRQTTQTQFR+MTTAGKA
Sbjct: 661  THHNSYALADGEHFIVDPDKLSSTIVDLEKILKLIEGLDYSTLRQTTQTQFRDMTTAGKA 720

Query: 722  LLSKSNLRQGEKQKFLQEAQFFLGRVDLDKAIAKAEKALVTKKATKNGHLLERSINKAVL 781
            LLSKSNLRQGEKQKFLQEAQFFLGRVDLDKAIAKAEKALVTKKATKNG LLERSINKAVL
Sbjct: 721  LLSKSNLRQGEKQKFLQEAQFFLGRVDLDKAIAKAEKALVTKKATKNGQLLERSINKAVL 780

Query: 782  AYNNSAIKKANVKRLEKELDLLTDLVEGKGPLAQATMVQGVYLLKTPLPLPEYYIGLNVY 841
            AYNNSAIKKANVKRLEKELDLLT LVEGKGPLAQATMVQGVYLLKTPLPLPEYYIGLNVY
Sbjct: 781  AYNNSAIKKANVKRLEKELDLLTGLVEGKGPLAQATMVQGVYLLKTPLPLPEYYIGLNVY 840

Query: 842  FDKSGKLIYALDMSDTIGEGQKDAYGNPILNVDEDNEGYHTLAVATLADYEGLYIKDILN 901
            FDKSGKLIYALDMSDTIGEGQKDAYGNPILNVDEDNEGYH LAVATLADYEGL IK ILN
Sbjct: 841  FDKSGKLIYALDMSDTIGEGQKDAYGNPILNVDEDNEGYHALAVATLADYEGLDIKTILN 900

Query: 902  SSLDKIKAIRQIPLAKYHRLGIFQAIRNAAAEADRLLPKTPKGYLNEVPNYRKKQVEKNL 961
            S L ++ +IRQ+P A YHR GIFQAI+NAAAEA++LLPK
Sbjct: 901  SKLSQLTSIRQVPTAAYHRAGIFQAIQNAAAEAEQLLPK---------------------- 939

Query: 962  KPVDYKTPIFNKALPNEKVDGDRAAKGHNINAETNNSVAVTPIRSEQQLHKSQSDVNLPQ 1021
                                    ++++   + N++          ++S  + ++ +    LP+
Sbjct: 940  ----------------PGTHSEKSSSSESANSKDRG------LQSNPKTNRGRHSAILPR 977

Query: 1022 TSSKNNFIYEILGYVSLCLLFLVTAGKKGK 1051
               T SK +F+Y ILGY S+ LL L+TA KK K
Sbjct: 978  TGSKGSFVYGILGYTSVALLSLITAIKKKK 1007
```

SEQ ID 800 (GBS97) was expressed in *E.coli* as a His-fusion product. SDS-PAGE analysis of total cell extract is shown in Figure 17 (lane 12; MW 113.4kDa).

```
12020          ------------------------------------------------------------
12018          ------------------------------------------------------------
12022          TTTTCAGTCATTAGGCT-------------------------------------------
```

It will be understood that the invention has been described by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention.

TABLE I – THEROETICAL MOLECULAR WEIGHTS FOR GBS PROTEINS

GBS #	expected mol. weight (dalton)		
	GST-fusion	His-fusion	Native
1	78425	53460	49720
2	40035	15070	11330
3	90305	65340	61600
4	43115	18150	14410
5	158835	133870	130130
6	39265	14300	10560
7	44985	20020	16280
8	56315	31350	27610
9	50265	25300	21560
10	96465	71500	67760
11	91515	66550	62810
11d	85905	60940	57200
12	64455	39490	35750
13	40475	15510	11770
14	33325	8360	4620
15	44765	19800	16060
16	73475	48510	44770
17	46745	21780	18040
18	54335	29370	25630
19	46085	21120	17380
20	47625	22660	18920
21	56535	31570	27830
21 long	66435	41470	37730
22	60055	35090	31350
23	60165	35200	31460
24	58405	33440	29700
25	50265	25300	21560
26	118245	93280	89540
28	63795	38830	35090
29	50595	25630	21890
30	44215	19250	15510
31	63795	38830	35090
31d	58735	33770	30030
32	40585	15620	11880
33	71495	46530	42790
34	69295	44330	40590
35	56535	31570	27830
36	59065	34100	30360
37	46965	22000	18260
38	61815	36850	33110
39	65225	40260	36520
41	75235	50270	46530
42	46745	21780	18040
43	58955	33990	30250
44	52355	27390	23650
45	43555	18590	14850
46	59835	34870	31130
47	84255	59290	55550
48	86455	61490	57750
48d	106695	81730	77990
49	59615	34650	30910
50	94155	69190	65450

51	47075	22110	18370
52	55435	30470	26730
53	110215	85250	81510
54	73365	48400	44660
55	36295	11330	7590
56	34865	9900	6160
57	51145	26180	22440
58	128805	103840	100100
59	99215	74250	70510
60	63575	38610	34870
61	68085	43120	39380
62	105485	80520	76780
63	64125	39160	35420
64	112745	87780	84040
65	72485	47520	43780
66	49715	24750	21010
67	120335	95370	91630
68	131225	106260	102520
68d	103065	78100	74360
69	53895	28930	25190
70	74465	49500	45760
70d	59725	34760	31020
71	56755	31790	28050
72	75565	50600	46860
73	72815	47850	44110
74	131225	106260	102520
74d	95475	70510	66770
75	114725	89760	86020
76	198875	173910	170170
77	78535	53570	49830
78	48835	23870	20130
79	58185	33220	29480
79d	50815	25850	22110
80	81835	56870	53130
81	89205	64240	60500
82	40475	15510	11770
83	62585	37620	33880
84	122645	97680	93940
85	70175	45210	41470
86	84035	59070	55330
87	44435	19470	15730
88	73365	48400	44660
89	143325	118360	114620
90	93495	68530	64790
91	88325	63360	59620
92	193595	168630	164890
93	95585	70620	66880
94	77435	52470	48730
95	60605	35640	31900
96	57195	32230	28490
97	138375	113410	109670
98	82055	57090	53350
99	60715	35750	32010
100	53015	28050	24310
101	59395	34430	30690
102	40695	15730	11990
103	56975	32010	28270

104	120005	95040	91300
105	179735	154770	151030
105dNterm	127265	102300	98560
105dCterm	81285	56320	52580
106	85795	60830	57090
107	89535	64570	60830
108	64565	39600	35860
109	75125	50160	46420
109d	70725	45760	42020
110	53895	28930	25190
111 / 190	60165	35200	31460
112	63905	38940	35200
113	59175	34210	30470
114	51915	26950	23210
115	98225	73260	69520
116	73475	48510	44770
117	47515	22550	18810
118	42235	17270	13530
119	109225	84260	80520
120	71385	46420	42680
121	65115	40150	36410
122	46855	21890	18150
123	68305	43340	39600
124	54115	29150	25410
125	57305	32340	28600
126	56865	31900	28160
127	80845	55880	52140
128	39925	14960	11220
129	43775	18810	15070
130	82275	57310	53570
130d	63245	38280	34540
131	89755	64790	61050
132	49055	24090	20350
133	54445	29480	25740
134	42015	17050	13310
135	65225	40260	36520
136	54885	29920	26180
137	63465	38500	34760
138	40145	15180	11440
139	38165	13200	9460
140	43445	18480	14740
141	49935	24970	21230
142	79745	54780	51040
143	33545	8580	4840
144	49165	24200	20460
145	63025	38060	34320
146	107025	82060	78320
147	156965	132000	128260
148	41905	16940	13200
149	62365	37400	33660
150	54665	29700	25960
151	50412	25447	21707
151L	50045	25080	21340
152	45535	20570	16830
153	46965	22000	18260
154	101525	76560	72820
155	62585	37620	33880

156	61265	36300	32560
157	74025	49060	45320
158	52025	27060	23320
159	41025	16060	12320
160	82825	57860	54120
161	95365	70400	66660
162	42015	17050	13310
163	69405	44440	40700
164	42345	17380	13640
165	43555	18590	14850
166	38055	13090	9350
167	50375	25410	21670
168	32555	7590	3850
169	43445	18480	14740
170	64015	39050	35310
170d	59945	34980	31240
171	49825	24860	21120
172	62365	37400	33660
173	96795	71830	68090
174	45095	20130	16390
175	59175	34210	30470
176	55435	30470	26730
177	66215	41250	37510
178	62365	37400	33660
179	58515	33550	29810
180	37615	12650	8910
181	63685	38720	34980
182	90085	65120	61380
182d	87225	62260	58520
183	57855	32890	29150
184	46415	21450	17710
185	40695	15730	11990
186	85685	60720	56980
187	56205	31240	27500
188	61595	36630	32890
189	60165	35200	31460
191	116705	91740	88000
192	69625	44660	40920
193	98005	73040	69300
194	49385	24420	20680
195	81065	56100	52360
195L	147615	122650	118910
195L N-term	91405	66440	62700
196	69515	44550	40810
197	99325	74360	70620
198	73805	48840	45100
199	158285	133320	129580
200	132325	107360	103620
201	74538	49573	45833
202	157295	132330	128590
203	61705	36740	33000
204	39705	14740	11000
205	55985	31020	27280
206	56645	31680	27940
207	44765	19800	16060
208	59725	34760	31020
209	62145	37180	33440

209d	56425	31460	27720
210	60935	35970	32230
210d	53675	28710	24970
211	64895	39930	36190
212	60825	35860	32120
213	45205	20240	16500
214	38935	13970	10230
215	45205	20240	16500
216	91515	66550	62810
217	36075	11110	7370
218	81065	56100	52360
219	56535	31570	27830
220	54555	29590	25850
220	50155	25190	21450
221	41465	16500	12760
222	47405	22440	18700
223	42895	17930	14190
224	45865	20900	17160
225	56645	31680	27940
226	44875	19910	16170
227	46195	21230	17490
228	46525	21560	17820
229	35855	10890	7150
230	51915	26950	23210
231	60935	35970	32230
231d	58735	33770	30030
232	41795	16830	13090
233	35635	10670	6930
234	43115	18150	14410
235	58295	33330	29590
235d	48395	23430	19690
236	46525	21560	17820
237	44215	19250	15510
238	59725	34760	31020
239	63905	38940	35200
240	51475	26510	22770
241	45095	20130	16390
242	43225	18260	14520
243	119455	94490	90750
244	48065	23100	19360
245	48615	23650	19910
246	49605	24640	20900
246d	45975	21010	17270
247	58955	33990	30250
248	92505	67540	63800
248d	70835	45870	42130
249	103835	78870	75130
250	136505	111540	107800
251	52135	27170	23430
252	51695	26730	22990
253	74245	49280	45540
254	59615	34650	30910
255	69075	44110	40370
256	47845	22880	19140
257	60495	35530	31790
258	67975	43010	39270
259	79415	54450	50710

260	48175	23210	19470
261	55765	30800	27060
262	75345	50380	46640
263	63465	38500	34760
264	47185	22220	18480
265	56315	31350	27610
266	51365	26400	22660
267	88655	63690	59950
268	50265	25300	21560
269	60495	35530	31790
270	59285	34320	30580
271	56315	31350	27610
272	118355	93390	89650
272d	98885	73920	70180
273	70945	45980	42240
274	56205	31240	27500
275	47515	22550	18810
276	147945	122980	119240
277	87005	62040	58300
277d	75675	50710	46970
278	52245	27280	23540
279	79415	54450	50710
280	88655	63690	59950
281	74465	49500	45760
281d	71495	46530	42790
282	44765	19800	16060
283		20240	16500
284	67645	42680	38940
285	57525	32560	28820
286	41355	16390	12650
287	61045	36080	32340
287d	57085	32120	28380
288	53675	28710	24970
288d	51035	26070	22330
289	65005	40040	36300
289 long	71825	46860	43120
290	47405	22440	18700
291	63795	38830	35090
292	103505	78540	74800
293	115935	90970	87230
293d N-term	73805	48840	45100
293d C-term	70835	45870	42130
294	75785	50820	47080
295	89425	64460	60720
296	60385	35420	31680
297	100205	75240	71500
298	54335	29370	25630
299	62255	37290	33550
300	130895	105930	102190
301	54885	29920	26180
302	80075	55110	51370
303	53235	28270	24530
304	75125	50160	46420
305	78645	53680	49940
306	67975	43010	39270
307	86675	61710	57970
308	59285	34320	30580

309	62695	37730	33990
310	58845	33880	30140
311	76445	51480	47740
312	64785	39820	36080
313	65995	41030	37290
314	52135	27170	23430
315	51695	26730	22990
316	41795	16830	13090
317	179295	154330	150590
317d N-term	115935	90970	87230
317d C-term	92160	67402	63360
318	70065	45100	41360
319	61925	36960	33220
320	57965	33000	29260
321	83705	58740	55000
322	76628	51663	47923
323	86345	61380	57640
324	86345	61380	57640
325	82605	57640	53900
326	91515	66550	62810
326L	172695	147730	143990
326L N-term	113955	88990	85250
327	279175	254210	250470
327d N-term	139915	114950	111210
327d C-term	167965	143000	139260
328	97602	72637	68897
329	113955	88990	85250
330	83595	58630	54890
331	60825	35860	32120
332	75675	50710	46970
333	63465	38500	34760
333d	57965	33000	29260
334	38275	13310	9570
335	43555	18590	14850
336	67645	42680	38940
337	75235	50270	46530
338	54995	30030	26290
339	76665	51700	47960
339d	72925	47960	44220
340	86565	61600	57860
341	38385	13420	9680
342	61595	36630	32890
343	60385	35420	31680
344	55875	30910	27170
345	40585	15620	11880
346	53895	28930	25190
347	55325	30360	26620
348	58405	33440	29700
349	98335	73370	69630
350	53895	28930	25190
351	82165	57200	53460
352	111315	86350	82610
352d	105485	80520	76780
353	55325	30360	26620
354	42345	17380	13640
355	52135	27170	23430
356	59065	34100	30360

357	40255	15290	11550
358	60495	35530	31790
359	78865	53900	50160
360	73695	48730	44990
361	109005	84040	80300
362	125945	100980	97240
362d N-term	63355	38390	34650
362d C-term	91295	66330	62590
363	53125	28160	24420
364	75015	50050	46310
365	102075	77110	73370
366	68415	43450	39710
367	76885	51920	48180
368	44765	19800	16060
369	142115	117150	113410
370	94595	69630	65890
371	65555	40590	36850
372	55105	30140	26400
373	50265	25300	21560
374	57525	32560	28820
375	66875	41910	38170
376	48065	23100	19360
377	73805	48840	45100
378	58955	33990	30250
379	68855	43890	40150
380	47405	22440	18700
381	66875	41910	38170
382	50815	25850	22110
383	57085	32120	28380
384	77985	53020	49280
385	75675	50710	46970
386	39485	14520	10780
387	54555	29590	25850
388	45645	20680	16940
389	43005	18040	14300
390	62255	37290	33550
391	54775	29810	26070
392	71385	46420	42680
393	55765	30800	27060
394	59725	34760	31020
395	72375	47410	43670
396	34865	9900	6160
397	113625	88660	84920
397d	100865	3740	72160
398	56755	31790	28050
399	55435	30470	26730
400	74135	49170	45430
401	59395	34430	30690
402	78095	53130	49390
403	64455	39490	35750
404	61595	36630	32890
405	45975	21010	17270
406	36955	11990	8250
407	82715	57750	54010
407d	71715	46750	43010
408	45315	20350	16610
409	70395	45430	41690

409d	59600	34842	30800
410	62475	37510	33770
411	41355	16390	12650
412	35965	11000	7260
413	59175	34210	30470
414	50375	25410	21670
415	46195	21230	17490
416	42455	17490	13750
417	77985	53020	49280
418	42125	17160	13420
419	47515	22550	18810
420	67755	42790	39050
421	62915	37950	34210
422	60165	35200	31460
423	74245	49280	45540
424	89975	65010	61270
424	77325	52360	48620
425	116045	91080	87340
426	83815	58850	55110
427	41135	16170	12430
428	55325	30360	26620
429	59175	34210	30470
430	53785	28820	25080
431	54005	29040	25300
432	65665	40700	36960
433	40915	15950	12210
434	44545	19580	15840
642	91845	66880	63140
643	78975	54010	50270
644	49605	24640	20900
645	59725	34760	31020
646	61595	36630	32890
647	55875	30910	27170
648	59835	34870	31130
649	76115	51150	47410
650	51475	26510	22770
651	53345	28380	24640
652	49715	24750	21010
653	44655	19690	15950
654	51255	26290	22550
655	65995	41030	37290
656	57525	32560	28820
657	62805	37840	34100
658	60165	35200	31460
659	60275	35310	31570
660	71495	46530	42790
661	60605	35640	31900
662	62695	37730	33990
663	89535	64570	60830
664	45315	20350	16610
665	41135	16170	12430
666	47075	22110	18370
667	53162	28197	24457
668	43555	18590	14850
669	48505	23540	19800
670	45315	20350	16610
671	36940	12182	8140

672	40130	15372	11330
673	41450	16692	12650
674	45300	20542	16500
675	55970	31212	27170
676	65650	40892	36850
677	54320	29562	25520
678	77750	52992	48950
679	60480	35722	31680
680	64440	39682	35640
681	93040	68282	64240
682	84790	60032	55990
683	15950	44655	19690
684	11880	40585	15620
685	16280	44985	20020
686	21340	50045	25080
687	9350	38055	13090
689	55105	3740	26400

TABLE II – PRIMERS USED TO AMPLIFY GBS*nnn* PROTEINS

Forward primers begin 5'-GGGGACAAGTTTGTACAAAAAAGCAGGC-3' and continue with the sequences indicated in the table below; reverse primers begin 5'-GGGGACCACTTTGTACAAGAAAGCTGGGTT-3' and continue with the sequences indicated in the table. The primers for GBS1 are thus:

Fwd: GGGGACAAGTTTGTACAAAAAAGCAGGC**TCTCAATCTCATATTGTTTCAG**

Rev: GGGGACCACTTTGTACAAGAAAGCTGGGTT**ATTTTTAGACATCATAGACA**

The full forward primer sequences are given in the sequence listing as SEQ IDs 10968-11492. The reverse primer sequences are SEQ IDs 11493-12017.

GBS	Forward	Reverse
1	TCTCAATCTCATATTGTTTCAG	ATTTTTAGACATCATAGACA
2	TCTAATTACATTATTACATTTTTG	GGGAATGCCTACAAA
3	TCTGATACTAGTTCAGGAATATC	TTTTTTACTATACTTTTTGT
4	TCTGATACAAGTGATAAGAATACT	TTCCTTTTTAGGCTTACT
5	TCTATTTTTCTTCATAGTCCAC	ATTAGCTTCATTTGTCAG
6	TCTGAATGGGTGTTATTAACTC	AGTTTCTTCTTTAAAATCAT
7	TCTACAAATTCTTATTTTAGCAA	CTCTGAAGCTGTAAAACC
8	TCTGTATCAGTTCAGGCGT	TTTATCAATGTTTGAAACG
9	TCTGCTGCTCTAGGACAAC	TAGTAAATCAAGTTTTTGCA
10	TCTTTTGTTGTTGCCTTATT	ATCCCTTCTATTTTCGA
11	TCTCCACCTATGGAACGT	ATGTAGTGACGTTTCTGTG
11d	TCTCAGAAAGTCTATCGGG	ATGTAGTGACGTTTCTGTG
12	TCTAGTGAGAAGAAAGCAAAT	ATTGGGTGTAAGCATT
13	TCTTCTTGGAATTATTGGAG	CTTAACTCTACCCGTCC
14	TCTGCAATGATTGTAACCAT	TTTTCTCTTATTAAAGAATT
15	TCTGCATCTTATACCGTGAA	ATACCAGCCGTTACTATT
16	TCTGCCGAGAAGGATAAA	TTTAGCTGCTTTTTTAATG
17	TCTGTTTATAAAGTTATTCAAAA	AAATACTACATTTACAGGTG
18	TCTAAGCCTAACAGTCAACA	TTGGTTATTCTCCTTTAAT
19	TCTGATGATAACTTTGAAATGC	ATTATATTTTTGGATATTTC
20	TCTGCAGTGATTGCAAGTC	GGGCTTTTTCTTAAAAA
21	TGTGCTGCATCAAAC	GTTGGCATCCCTTTT
21 Long+A527	TGTGCTGCATCAAAC	CTTTTGATGGGATTGG

22	TGTACTAAACAAAGCCAG	TTGATTTAACGATTTGA
23	TGTCAATTAACCGATAC	TTTATCTCCTCTAAAATAATG
24	TGCTCAAATGATTCAT	CTTTGATAAGTCAGACCA
25	TCTAAAAGTTCACAAGTTACTACT	GTAACCCCAAGCTGAT
26	TCTAGTCATTATTCCATAAAATT	TGATTTTGCAATATCAA
28	TCTAATCATATGCTGATTGAG	TTTTTGTAATTTAAGTACTAA
29	TCAGTTTGGATGTTAAC	TTCTTTTATATTAAGAGCTT
30	TCAACAAATGCAGATG	ATTCGGATAAATGTAGC
31	TGTTTTGTCATTATTGATAG	TCCATTTTTATCCTCAC
31d	TCTCTAACTTGGTTTTTATTAGA	TCCATTTTTATCCTCAC
32	TCTGGTTTAAAAGTGACTGAA	ATGACCTCTACTTTCCA
33	TCTCATCATTTAGGTAAGGAA	CTTGTAATCACTTGGAC
34	TCTGTTAGTAATCGCTACAATC	ATTAATCATGGTATTGGT
35	TCTAATCAAGAAGTTTCAGC	CCATTGTGGAATATCA
36	TCTCGAGTTTTAGCGGATA	TTTGTAAAGCAGTTCTT
37	TCTGTATTATTTTACCAATCACA	ATCATTCATATGATCTCTAGA
38	TTAGGAGTGGTAGTTCAT	ATTTTGATTGATTCTACTC
39	TTTTTATTGTTAGTATTAGC	TTTTGTTTTTTTCAAATA
41	TCTGTTTATCTAGCGGTTAGA	ATCTTCAACGTCCTCC
42	TATAACAGTTTAGTTAGAAGTC	AAAGTCAAAGGAAACTT
43	TTTAAAGGGTTTACATATT	TTCTTTATCTAATTTATAATAG
44	TTTAATACAATTGGTCG	TTGCAATGTTTTTTCT
45	TCTATGGAAAAAATTAGGATT	TAAACTTTGGATAATCTGT
46	TCTAGAGATGAGCAAGAAATA	GTTGAAATTTTGATATGA
47	TCTCAACAGATAGGTCTTTATAA	CTCCTTTACTATATAGCTAACT
48	TTTCTCTATAATTACTTCAAT	TTGTTTGTGAAGTAAAAC
49	TCTAATAAGGCATTATTAGAGG	TGATAATATCTCCATATTTT
50	TCTACACATTTAGTTGACTTAAC	GCATTGGCGCCATA
51	TCTAGTAAACAACACATTTATCTA	TTCTACACGACTTTTATTC
52	TCTCAAGAAACTCATCAGTTG	AAGACCTCCTCGAGAT
53	TCTGCAGAAGACATTGTTACA	TGTTTTTTCTTTCTGTTG
54	TATAATTTTTCGACTAATGA	TGGATTAGTTTGACCTG
55	TCTGACACAGTGTCTTATCCT	TTTATCGTAAGCACTTAGG
56	TCTGTGGAGCAAGTGGCCA	CTCCTTCCAGGCATCG
57	TCTCAAGAACTAAGTAACTTTGA	GTAAAAGTATCTTAAATAGTCA
58	TCTACTGAAACGTTTGAAGG	TGCCATTCCTCCTCT
59	TCTGATGAAGCAACAACTAA	TGTTACCTTTTTATTTTCT
60	TCTAATAAAGATAATCAAAAAACT	TTTTTCATGCGATTGA
61	TGTTTCTTTTTTATTCCA	GAGACGTTTCTTATACCTT
62	TATTACTTTGATGGTAGTTT	TGTACCATATGTTCTCTCT
63	TCTGTTCAATCATTAGCAAA	AAAAGTTGGACTACTTTC
64	TTTAAAGGTAATAAGAAGTTG	TCGTTTTCCACCC
64d	TCTAGTCAAGTTGACTCTGTTA	TCGTTTTCCACCC
65	TCTCAAAACCAGGTGACTG	ATTTGGGTAAATATAGTAAA
66	TTAAGATTTTATAACAACGA	TTTACGACTAACCTCAAC
67	TCTAATGTTTTAGGGGAAA	AATTCCTTTTGGTGG
68	TCCCAAAAGACTTTTG	GGCAGAATACACCTTC
68d	TCCCAAAAGACTTTTG	GGCTGACGTCGACGCA
69	TCTAAAGTTTTAGCCTTTGA	AACTCTCTTAATATATTCTTCT
70	TCTGAAATGGCTTTAG	GTCTTTTTCAATATTCTGT
70d	TCTACTAACTTATTGAGTAGAATCA	GTCTTTTTCAATATTCTGT
71	TGTAGCTCAAAATCTCAT	CTTCTCCTTAGGAGTAACG
72	TCTAGTTTATCTATTAAAGATGCC	ATTATTATCAATTAATAACTCTT
73	TCTATCAAAGAGGCGGTAA	GTCAAACATACTTCCAAA
74	TCTAAAGAGGATAAAAAGCTAG	TTTCGTCGTATAAGCA
74d	TCTAGTGTTTCAGGTAGTAGTG	TTTCGTCGTATAAGCA
75	TCTAAAAAATTAAAACACTCAA	TGTCCTCATTTTTTCAG

76	TCTGATGAAGTTACAACTTCAG	AATACTTGCTGGAACAG
77	TTATTCCAAAGTAAAATAAA	GTCTTTCTTCAATTTTGG
78	TCTCATAACCATCACTCAGAACACATGT	GTCGTGATTTTTATGAGT
79	TCTCCCAAGAATAGGATAAA	CCCAAACTGGCATAAC
79d	TCTAGTCAGTATGAGTCACAGA	CCCAAACTGGCATAAC
80	TCTGCAGAAGTGTCACAAGA	TGAAGGACGTTTGTTG
81	TCTTTTGATGGATTTTT	TTTTTTTAGTTTAAGGCTA
82	TCTACAAATGAAAAACGAAC	GTCCACCTTCCGAT
83	TCTGAAATTAAACTCAAAAATATT	AACATTGTTTTTCCTTTC
84	TCTCATACTCAAGAACACAAAA	ATGGTGATGATGACCT
85	TCTCCTAAGAAGAAATCAGATAC	ATTAACATTTTGAGGGT
86	TCTGCAGAACTAACTCTTTTAA	TTTTGCAAAATCAACA
87	TCTGCGGATACATATAATAACTA	GAATAAATAACTGTATTTTTT
88	TCTTACCAAAAAATGACG	ATTTTCATTAATTTCCTCT
89	TCTGAAGAGCTTACCAAAAC	GATAGCTAATTGGTCTGT
90	TCTAGATATACAAATGGAAATTT	TAAAAGATGAGCTTCTCG
91	TCTAAAAAAGGACAAGTAAATG	AATTTCAATATAGCGACG
92	TCTGATTCTGTCATAAATAAGC	CTTGTTTGTCTTTACCTT
93	TCTGAATTTTCACGAGAAA	ATTATCCTTCAAAGCTG
94	TACCAATTAGGTAGCTATAA	TGTGTCATATAATGTAACCA
95	TCTGTTAATACAAAAACACTTCT	TGATCTTAATTTTCGAG
96	TCTGGTCAGTCTAAAAATGAAG	CCAAACAGGTTGATCT
97	TCTAGCCAGGAGGTATATG	ATTTACATCAGACTGTGAC
98	TCTGAAACTATTAATCCAGAAA	TTTATGGCCAATAACA
99	TCTACAAGTATGAACCATCAA	TTTTTTAGTAGTTGTCAATT
100	TCTAAGGGGCCAAAAGTAG	GTAAGCTGAATTTTCGA
101	TCTATTACTTTAGAAAAATTTATAGA	ACGAGAGTGGTTATTGG
102	TCTGCCTTTTACTTTGGCA	TTTCTTCACTCTTTCTAGAG
103	TCTATTTTTTCCTTGATCAT	CGGCCAGTTTTTTTCTT
104	TCTGGTGAAACCCAAGATA	AACACCTGGTGGGCGT
105	TTAACAATTCATGGACC	ACTATTTCTAATTGCTCTG
105d	TTAACAATTCATGGACC	TGGTCCCGGTGCGCCA
105d	TCTCAAGGACCTCCCGGTG	ACTATTTCTAATTGCTCTG
106	TCTCAAAATCAAAATTCACA	CTTAGCAGATTCATCCC
107	TCTCTGGAGCCTTTTATTT	TTTACTATTTGAAAATTGG
108	TCTGGTAATCGTTCAGATAAG	TTTCATAGGAACTTGTATT
109	TCTATCCAGCAGATCAACT	GTCCACACCTGCGACT
109d	TCTAAACGGGTTCGCTATG	GTCCACACCTGCGACT
110	TCTGTAAAATTAGTATTCGCAC	TTTACCTAAGTAATATTCTGA
111.19	TCTGTTAGCGTTGATAAGGC	TCCCCGTCTTTTTTGT
112	TCTACAATTAAAAATCTCACTG	GTCGTAATCATAAAAGCC
113	TCTAGTAAAATCAAAATTGTAACG	TTCATAACGAACCATAAC
114	TCTAATCTTTTAATTATGGGTT	TTTGAGTTCTAGCAACG
115	TTTCAATACTATTTAAAAGG	TTTTTTATCTTCTTCTTGC
116	TCTACCGAGGAGCCATTAA	TTTTAAAACCTGGTAAAC
117	TCTGAACAATCACAAAAAACA	TCAGCTCGTACTGTTT
118	TCTATGGTGACGGTGCTGG	GTCCTCCTCAATTGGT
119	TCTAGTCAGCCGGTAGGGG	CTCTTTTATACGCGATG
120	TCTGGTGGAGCATTTGCTA	GTTATTTGCTCGTTGTT
121	TCTAATAAAGATAATCAAAAAACT	TTTCTCAAATGTTTTCAT
122	TCTGCTGCCACCAAGAAAG	TTTCAAATGATCTACAGC
123	TCTACAACAAATGTAATGGC	GGCTAGTGTCTGTCCG
124	TCAATGAATTTTTCATTT	ACCATCTATTTTTACCCC
125	TCTACAAAATATCAGCGAATG	AGAACCCGCACTCTCA
126	TCTACTAAGCAAGCAATGTC	GAACGCAACGGCTGCT
127	TCTACAAAAGAATATCAAAATTAT	TTTCATATCAAAAACTATCG
128	TCGACTAATTCGTTAAA	TTCTTTATCTCTTAATGCTT

129	TTTGAAATAGTATTGGAAA	CACAACAGTTATTTTTTCA
130	TCTATATTTTCTATTTTTTATTATGT	AGGCCCTTCTGAGTAG
130d	TCTAAAAAAACAACTTCACAAC	AGGCCCTTCTGAGTAG
131	TCTAAAACAGATATTGAAATAGC	AAATAATCCAATGGCTG
132	TCTATTAAATATTATCATTTGCA	CTTTTCAAGCTTTTTCC
133	TCTGCTTTACGGAACCTTG	AAAATGATCAGTTTGAGG
134	TCTACTATTTCTCAACAACAATAC	TTTTTGGCTTAAGAAAG
135	TCTGAAAAAAAGAGTAGTTCAAC	CTTACGATACATTTTAAATTG
136	TCTAATCAATTATCAGAAATCA	TTCTTTTTTTACTTTAGCG
137	TCTCAAGAGTATAAAACAAAAGAG	CCATTGCAATCCAGCA
138	TCTGCTGTATTTACACTCGTC	ATGTTTATGGCTTGCT
139	TCTGGCGGCAAGATAAAAT	TTTTTGATAAATCCCC
140	TCTGATGGGTTAAAGAATAATG	ATATGTGTATTCATCCTTT
141	TCTGATGTTGTAATTAGTGGAG	TACTTCTATTTTTCCATCTG
142	TTCGAATTAAGAGAAAGA	GTAATGCAATAAATCAAAA
143	TCTAGCTTTTTAGTGATTTCA	GGATTTTAGTTTCGCA
144	TATACGCATAGTGGAAC	CCCATTGATTTCGTCG
145	TCTGTTATTATCAGGGGCG	TACCTCTTTCAATACCAC
146	TCTGTTAGTCGTTCTCCGA	ATTACCGTTAGGTACTGTA
147	TCTGAGGAGCAAGAATTAAA	GGTATGGTTAACAGAATC
148	TCTATTCTAACAAAAGCAAGT	ATATACCCTAGACTTTTTGA
149	TCTAGTGGGCGTTCATGGA	AGGAGTTTTATTGATGATAT
150	TCTGATACCCCTAATCAACTA	AAATGATTGTGGAAAAA
151	TGCAGGAGCTGTCCGC	ATCAAAGAAGTTGACATTG
151 Long	TCTGTCCGCATTGGTAAAG	ATCAAAGAAGTTGACATTG
152	TCTAACTGCTTAGAAAATGAA	GTTAGATAAATTAACCAGTG
153	TCTAACAACTCCAGCA	CCCTTTGCTTCGTTGT
154	TCTGGAAAGGTCAGTGCAG	TTCCACAAGTCCGATT
155	TCTATTTTATTTTCAGATGAAC	TTGTTTGATTCGTCCT
156	TCTGCATCAGATGTTCAGA	ACTACCAAACTGCTGG
157	TCTAGTGACGTTGACAAATA	TTGTGTATTTTTAGTTAGGT
158	TCTATGACCATTTACTTCAATA	GTGGATAAAATTCGAAA
159	TCTCAAACTATTTTGACGC	CAGACTGACTAGGAGCT
160	TCTGATGAATATCTACGTGTCG	GACTTGTAATTGATTCGC
161	TCTGATGAGGTGGACTATAACA	GAAGGCACCACCACCT
162	TCTATTTTCTTGCTCTTAGTTG	GTTGTATAGATGAGTTAATCTG
163	TCTGAAACTGTCATTCAACTTG	ACGGTTTTTAAAGAATG
164	TATTTTTTAACAACAAAAAA	TTTTTCTTTATCTTCTGTG
165	TCTCCAATTTTTATTGGTTT	CGATTTTGTAAGAGCTT
166	TCTGCATCTTATACCGTGAA	CGACGAAGCTATTTCT
167	TCTACAATTTATATTGCTTGG	TAAGGCTTGCATTTTG
168	TCTGTTGGATTGATGTTGG	TTTTCCTAAAAATTTTCC
169	TGGAAACAAATCACAG	GGCATCTCCTAGCTTT
170	TCTGCAATAGTTTTTACTTTTTT	TGATAAAGGTAGTTCTACAC
170d	TCTGGTTCTTATCATTTAACAA	TGATAAAGGTAGTTCTACAC
171	TCTGCTAGACCCAAACAGT	TTTTAGATGTTTTTGTGG
172	TACACTCATATTGTTGAAAA	ATGATTGATAATTTTAAGC
173	TCTAATAGTACTGAGACAAGTGC	TGCTTTTTGATATGCC
174	TCTGCTTATGTCGTCAATTT	TAAAATAAAGTTCAGAAAAG
175	TCTGAATTACCTTCGTTTATC	TTTCTCCCTTGACTTTC
176	TCTAAACATCCGATACTTAATG	CTTTTTCTCAGATGCTT
177	TCTAATTATCCTTTTGCGA	GACATTGAAACGGAAT
178	TCTGGACTACGCGGAGTAT	TTTTATCAATGATGTTGA
179	TCTGCTATTGGAGCAGCTG	CATATGACGCAAACGC
180	TCTGATAAAGAAGGGATAGAGG	AGCCTCTTTTCTTGTT
181	TCTAAAGAAAAATCACAAACTG	ACGATTATCAACAAAGTT
182	TCTCAAAATAATAAAAAAGTAAAA	CATTCTTTTAAATACAAATC

182d	TCTCAAAATAATAAAAAAGTAAAA	GGGTTTGAAAGTTTTC
183	TCAAATGGTCAATCTAGC	TTTAACTTTAATTACTGGAAT
184	TCTAAGGATTCAAAAATCCC	TTTTTTAATAAGCTTCGA
185	TCTGGGCAACCATCTACAT	TTTTTTGTAAACTTCCTG
186	TCTCATTCACAGGATAGCA	CTTAGATACATTGTTTTTTTC
187	TCTGGACGAGGAGAAGTATC	CTTTCTTTTCTTACTTGC
188	TCACAATCTTCTCAAAA	TTTATTATTTTTAATACTTGAA
189	TCTGATAAGTCAGCAAACCC	CTTCAACTGTTGATAGAGC
191	TCTATCACGACATTACAGACT	TCCTTTAGCAGGAGCT
192	TCTAGATATTTAACTGCTGGT	GTTATACATGTTGTCTGAAG
193	TCTATAAAATATCAAGATGATTTT	CCAAATAATAACACGTTT
194	TTAGAAGTCAGAGAGCAG	GCTATCCCTTTCCAAT
195	TCTATTATGGAGACGGGTA	TGTATTTTTAATTTGTTTTC
195L	TCTTTGAATAATAAAGGTGTCG	TGTATTTTTAATTTGTTTTC
195LN	TCTTTGAATAATAAAGGTGTCG	CAAACTTTTAACATTTAATG
196	TCTATTTCCTCAAATTTTTACG	ATAGTGTAAGCTACCAGC
197	TCTAATTTTTATAAGCTCTTG	GTCATCATATTCCTGAAA
198	TCTGCGCTTAAAGAATTAA	TGTTCGGCGTAAGATT
199	TTTTTAAAAGAAATTGAAA	ATTGGTCATTTCTTGAG
200	TTTCGTAAATATAATTTTGA	AACAGATTTATTGGTTGG
201	TCTAGCGATACCTTTAATTTT	AGACTCATCAACTTTTTCT
202	TCTATGCTGATTAAGTCGC	GAACCCTGAAGGGTAG
203	TGTGGTAAAACTGGACT	CCAATTGTATTTTTCAAC
204	TCTAAGACAGGAGCACCCGT	ATTTATACTACCTGTTGAATC
205	TGCGAGTCAATTGAGC	TTTAAATTTGTAGTCTTTAATA
206	TCTACAAATACTTTGAAAAAAGA	CTCTTTTACTTTTCCAAAA
207	TCTAATTTATTTAAACGTTCCT	CCCTCCCTTAAGAGAA
208	TCTAAAAAGCGGCTAGTCA	TTGACGATGTTGCATC
209	TCTGGACAAAAATCAAAAATA	TTTCGAATTATTGTGACT
209d	TCTGGACAAAAATCAAAAATA	GTATTGTTGTTGCCTG
210	TCTGGAGGAAAATTTCAGAA	TTTTTGATTTCCCTTTC
210d	TCTACCTCATATCCTTTTATTT	TTTATAGTGTGTTTGCAA
211	TGTGGACATCGTGGTG	TTTGCTAGGAACTTTGA
212	TCTAAGACTAAAAAAATCATCA	TGATTCAATTCCTTTTC
213	TCTAAACACACCAGTAAAGAA	TTTTTCCTCTACTTTCTTA
214	TCTAAAAATAAAAAAATCTTATTT	TTTGCTCACCTCCACA
215	TTAATAAAAGGATTATTGTCA	CAATAACTTCTGTAAAATAAA
216	TCTGCTCGTTTAATACCACA	TTCACCCTTAAAATAATT
217	TCTAACACTAACATCCCTAGC	TGCATTTTTCCCTTCT
218	TCTAGAGGGAAGGTTATTTAC	CTCCAGTAAAGTATTAGTATTT
219	TCTATCAATAAAGTAACAGCTCA	GTGAGGTTTTGGTAATT
220	TCTAGAACACTATTTAGAATGATAT	TGCATATAAGTTTTTTAGC
220d	TACTATGCGAATCACAG	TGCATATAAGTTTTTTAGC
221	TCTAGTTTAGCATTGCAAAT	CTCATCTAAAGTGCTATCC
222	TCTACATTTTATAAAAAGACGG	CTCGTATTTAGGCAACT
223	TCTAAGAAAATACGAAGCTATAC	ATTGGATATGCCATAAA
224	TCTGGAGGAAATGAAATATTA	GACTTTTTGATGTTTACTTT
225	TCTGGTATGTCTAATAAGGAAAT	TTCTTTACTATAAACATCTTCA
226	TCTAACAAACTTATTACAGAAAA	AGCATTTAAAGTTGAATGT
227	TCTGTTTCATATGAAAAAGTCC	GTTAGTCTCTTCAAGATCA
228	TCTAGTAGAGGTATTTTTTTTACAA	AAGACCTACCGCCCAA
229	TCTGAACGTCGGGTAAGTC	TACTTCTTTCTCTTTCAATT
230	TTTTTAATCGATTTTATTT	CTTAGTGTTCCGATATGA
231	TCATTAATTATTCTTACGGT	TCTTGTTTTAAGAGCAGA
231d	TCTTTATACGTTGTTAAACA	TCTTGTTTTAAGAGCAGA
232	TGGCTAAGTAAGCATGAG	ATCATGTTTTCCCTCAA
233	TTCCCAGCTAGCTGTC	ATCTGATATATCCGTTTTAT

234	TCTATAGAAATTGCTGTATTAATT	TTTTTTGTCTCCTTTTTTA
235	TCTATTCGATTTCTTATTCTTG	AAAGACACGATAAACATAAG
235d	TCTGACTCAACCACAGTCTC	AAAGACACGATAAACATAAG
236	TCTGCAGACCTTACAAGTCA	ATTTGCAACTTCTTGTATA
237	TCTATTGTATTTGCTATTGCA	TTTAAAAGTATCCTTAAATAAG
238	TCTGATATTTTTTCAGCTATTGA	CTTCCTCCTCAATAGTTG
239	TCTGTTAGTGCTGCTATTGAA	TTCTCCTCCCCCATTA
240	TCTAAGAAGCTTACTTTTATTTG	ATCCAAACGAGTGAAAT
241	TCAAAAGGATATTCAAGA	AGGTGTTGTTGTATTTTC
242	TCTCATAATATATTAAGATTTTTAGG	CTTTCTAAGTTTATTAAACATA
243	TCTATTCTTGGTCAAGATGT	GGCATCTGTTACCTTG
244	TCTCATGAAAATGTTAAAAAAG	AAACAACTCCATTATTTTT
245	TCTAAGTCAACGGTAACAAA	TAAACGTTGAAGAGCAT
246	AGGAAACGTTTTTCCT	CTTATCATATCTTGTTAAATCA
246d	TCTAACCATAAGGGAAAAGTA	CTTATCATATCTTGTTAAATCA
247	TCTGCTAAACAATTAATTGGT	TTGCCATGGGTTATAG
248	TCTTTGATGGTGTTGTTATTC	AGAATTAAAATTTTCATGC
248d	TCTAAAACTTATTTGTCAAATG	AGAATTAAAATTTTCATGC
249	TGGGCTTACCATACTG	TTTTTTAGATGTTTTATGTG
250	TCTGGCCTTAATCTTAAGC	CTCTTTTACTTTAGCTTCA
251	TCTCAATATTTTTTGAAACAAG	TTTCAAACTCCAGCCA
252	TTTATTTCAGGTTATATCAA	GGAGTGCCTTTCTACT
253	TCTGAAAATTGGAAGTTTGC	TTCATATCGTAAAGCATC
254	TCTATTGAAAAGGGAGTTG	ATCGTCAACCTTAACG
255	TCTATTGTTGGTAGAGAAATCA	TTTTACTTGACGTCTCAC
256	TATCATGTAAAAATTGATCA	GTCTTCCATTAATATTCCC
257	TCTGATTTTTTATACAAAGGAGG	CCAATTATTTTGAAAGTTC
258	TCTGAACGTTATACAGATAAAATG	ATTTTTTTGAATAATATAATCC
259	TCTCTTTCTCGTAAAAAAGAG	TTTATTATCAGAAAAGGC
260	TCTACTCTTGTCTTAGTTGTTTAT	ATTCAAAAAATTTTTCAA
261	TCTATAAAGAAAGCTGAAAATC	CGAAACGTCAGGTAAA
262	TCTATAAAAAATGCTATAGCATA	ACTTATTTTTGATAATATTTCTT
263	TCTCAGCCTTCTAAACTACTTC	ATCAGCATTTCTACGAA
264	TCTGATTTGTTTAGCATGTTG	ATGTAGACTCCTAATGATTT
265	TCTCTTGCTTCCCTGATTT	TTTACTGTTCCTTTCGC
266	TCTCATCAATCAAATCATTATC	GAGATTAATTTGATTATATTTT
267	TCTATCTTTATTATCGGACAA	AACATCATTTCCTCCC
268	TCTAAAGAATTTATTAAAGAATGG	GTTGATAGTTCCAAAACG
269	TCTGCAGATGATGGTGGTT	TAAATGTGTTCCTACTAAATT
270	TTAAATGATGCAATAACAA	CATCAATAGCCGAGCTG
271	TTGCTGGATTATCCTC	TTTATTTTCCAAATGACA
272	TCTGTATTTATGGCAAATAAGA	TTCACTCGGAGTTGGAG
272d	TCTATGAGTTCTCTGGAAGTT	TTCACTCGGAGTTGGAG
273	TCTGGTGTCCTCAACTCTG	AATGTAAATGACAAAGGTA
274	TCTGTTCATGATTTTGGTGA	GTTTTTTAATGGTTTGC
275	TCTGGGGTTTGGTTTTATA	TTTATCATAAGCATCTAGAC
276	TCTCAATCAGACATTAAAGCA	CTGATCTCTTGTTGATGC
277	TCTATTTGGAGGGGGGAAA	AAGCAGGGGAGCAATA
277d	TCTACCAAATTTGACTGGG	AAGCAGGGGAGCAATA
278	TCTGTTACGTTTTTCTTAT	CTGAGCAACACCTGTC
279	TCTAAAAAGAAAAGTTTAATTAGC	GGCAATTTTGTGGCAA
280	TTTGATTTTTTTAAGAAAA	TTGCTTAGTTAATGGCT
281	TCTAAGAAATTAATTATAGGTATTT	AGGCGTTGAATATAATTC
281d	TCTGGTTTTTCGTTTTTGA	AGGCGTTGAATATAATTC
282	TCTCTATTCTCAGATGAAACAA	CTTTTCAACTCCAAACA
283	TCTGTTAAATTAAAATCGTTACTG	GAGTTGTCTTTTTTTGTC
284	TCTATGCAACGATTAGGAC	GCAATCACAATTGACAT

285	TTAGGTGAAAGCAAATC	CTTTGTCTGCTTCACTT
286	TCTGGAGGATTTTATATGAAAG	TTGTATCTTCTCCTGACC
287	TCTGCACACACACCTACTAGT	TTGGTTAATCGTCTTG
287d	TCTAACAATCGTTCAAAGC	TTGGTTAATCGTCTTG
288	TCTAAAAAGTTTTTAAAAGTTTT	TTTAGTTACTTTCATAAATGG
288d	TGGAATAATCATCAGTCA	TTTAGTTACTTTCATAAATGG
289	TCTCAATCTAAAGGGCAAA	ATATAATTCCTCTAAAACTAGC
289L	TCTCAATCTAAAGGGCAAA	CCACTTCAAATTAACTAAC
290	TATTACTTATCAAAAGAAAAGG	ATTCCTTGAACACGAA
291	TCTCAAGTATTAAATGACAATGG	GTGCCATTCATTCTCT
292	TTGAATCGTAAAAAAAGG	TTGTCCTGTGAACTGTG
293	TCTATGGGTCTAGCAACAA	AGGGTTTATTTGTTGAAG
293d N-term	TCTATGGGTCTAGCAACAA	TCCTGATTTATCCACTG
293d C-term	TCTGTTACAGCTAAACACGG	AGGGTTTATTTGTTGAAG
294	TCTGGTCATTTTAGTGAAAAA	CAAAATACCTAAGCTAGC
295	TCTAGCGACATAAAAATCAT	ACGAACTTCCATAACC
296	TCTAAAGGTATTATTTTAGCG	GGCTTCTCCAATCAAA
297	TCTATTCAGATTGGCAAATT	TTGAGTTAATGGATTGTT
298	TCTACTAAATTTATTGTTGATTCA	TAGCGTTATTTCACTGTG
299	TTTGAAATACTTAAACCTG	TTTCTCCGCCCAGTCA
300	TCTGCTTCTACAAATAATGTTTC	CCGTTTATTCTTTCTACTG
301	TCTGTAATTAATATTGAGCAAGC	CATATCTGTTGCATCAAT
302	TCTGAAATCAACACTGAAATAG	AACTGGCTTTTTAGTCAG
303	TCTACAAGGCATATAAAAATTTC	TTTATTATTTAATTCTTCAATA
304	TCTAACGAAATCAAATGCCC	GTCTTTTAGAGCATCGA
305	TCTGGACGAGTAATGAAAACA	CTCTCCTCTAAGACTTTCG
306	TCTGGGAAAAAAATTGTTTT	TCCTTTTGTTACTTTTGC
307	TCTAAATTTACAGAACTTAACTTAT	TTTATCGCCTTTGTTG
308	ATGACACAGATGAATTTTA	ATGTTCAGGTTCTCCG
309	TTGCAACTTGGAATTG	TTCCATTATCTTCAAGTTA
310	TCTGCTAAAGAGAGGGTAGAT	CTCTTCTTCATTTTTCTTA
311	TCAATTATTACTGATGTTTAC	TTTTTTTAAGTTGTAGAATG
312	TCTACTGCAACTAAACAACAT	GTTTTTTGATGCTTCTTG
313	TCTAAACGTATTGCTGTTTTA	TTTACTACTTTGGTTGGC
314	TCTAAATTTTATCTTGTTAGACAC	GTGTGTCATTTTGACCT
315	TCTATAGGGGATTATTCAGTAA	TCCTTCAAGATCATTTAA
316	TCTACTGAACGAACATTCGA	ACCTCCTTTTCTTTCATT
317	TCTAATAAGCCATATTCAATAG	ATCTTCTCCTAACTTACCC
317d N-term	TCTAATAAGCCATATTCAATAG	ACTAGCTAGATTCTTAACGC
317d C-term	TCTGACTTGAATGGCAATAT	ATCTTCTCCTAACTTACCC
318	TCTATTGATTTTATTATTTCTATTG	GCCTCTTTCTCCAAAT
319	TTAAAACATTTTGGTAGTAA	ATGTCCTGTTATATCTTCTT
320	TCTACTATTTATGACCAAATTG	GCGTTGAATAATGGTT
321	TCTAAAAATAAAAAAGATCAGTT	TATTTCTTTAGTTTCTTCAA
322	TCTCAAGAAACAGATACGACG	TAATAAAAATTATATAAGAACCT
323	TCTGGTAATGAGTCAAAGAAC	TTCTGTCTTATAAGCATAAG
324	TCTGGAAGTAAATCAGCTTC	TTTTTTATAAGCATGTGTA
325	TCTGCTTGGCAACTTGTTC	ATGAGACATAAGGTCTTG
326	TCTGGCATCTCAGACTTACC	GTTGGAGCTCCTACTG
326L	TCTAAATTCAAATCTGGGG	GTTGGAGCTCCTACTG
326L N-term	TCTAAATTCAAATCTGGGG	CATTTCTTTGGTTAAAGC
327	TCTGGAGGGAAAATGAATC	TATCTCGAGTGCTATTTG
327d N-term	TCTGGAGGGAAAATGAATC	CTCTTCATCGACATAGTAA
327d C-term	TCTGGCAACTTCAAAGCAT	TATCTCGAGTGCTATTTG
328	TCTGACCAAGTCGGTGTCC	ATTTTACAGTAGTGGAGTTT
329	TCTAAATCAAAGACCTCTTCTA	TGTCCTCATTTTTTCA
330	TCTAATAAACGCGTAAAAATC	TTTAACAGTACGAACACG

331	TCTACCAGAACAGTAGCAAT	CCCCCTGTTTTTAAAAT
332	TCTACAAAAAACCTGTTATTAA	ACCCTCATATGATTCC
333	TCTATTGATATACAAAAAATAAAA	TTTAAAATAATGATACATCTC
333d	TCTGGATCATTGAGGGCAA	TTTAAAATAATGATACATCTC
334	TCTAATTTAGTAAAAGTGAATAGTG	TAACCCCGTCTCAACA
335	TCTGAAGAAGAAAAATATTTTGA	TATTTTCGTTTTCTCAAA
336	TCTCAGGTTGAAGTTGACTTA	TTTCTCCAAATAATCTCTC
337	TCTGAAACAGATTCGTTTGTA	CCTACTTTTAGTTTTAGAAGA
338	TCTGCTATAATAGACAAAAAG	GAAATCATAGCTTCCC
339	TCGAAACCGATTAAGAT	ACCTTTTACTTTTGGTAGT
339d	TCTCAAGTCATGCGCTATG	ACCTTTTACTTTTGGTAGT
340	TCTGGATTTCTCTATAATTACTTC	TTGTTTGTGAAGTAAAACG
341	TCTGGAAAACCATTGTTAAC	TAATTTAAAAATTGCATAAA
342	TCTCAGAAAATTGAAGGTATT	TTTCGTTACCATATCTAGA
343	TCTGAAATGCAAGTTCAAA	TAAATCATGGAAACTAGC
344	TCTGCACAACGCAGAATGT	AAAGCCCAACCTTCCG
345	TCTAAAAACCTGAATTGGG	GTTTCCACGTCCTTTC
346	TCTAATAAAATAGCTAATACAGAAG	AAGTTTATTCAAATCTGG
347	TCTATTGATATTCATTCTCATATC	AATGTAATGGTTTTTTAATA
348	TCTACTGGATCTAAAAAATTAGC	AGCTAAAATACCTAACCAG
349	TCTAAAGATCGCTTATATAATAAA	ATTTTTTAAACGACTCAT
350	TCTGCAAAAGATATAATTAAGGTT	AGCGGAACGGTGAATA
351	TCAGAAGATCAAAAACA	ATAATCTAAACTATCAGCTCT
352	TCTACTTTTTTTAAAAAGCTAAA	ATCTCCTATTGTAATTTTGA
352d	TCTGGTACAGATAGTAAATTTGG	ATCTCCTATTGTAATTTTGA
353	TCTACAATGTTAAAAATTGAAA	CACCTCTTTTGTCAGA
354	TCTATTAAAGAACTAAAAGAATTT	TTTGTTAGCGAGTAAGTC
355	TCTCGCTCACTACCTT	TTTATCATCCTCCTTAATAA
356	TCTAAATTCTATATTATTGATGATG	AAACGTTTTACTCTGTAAAA
357	TTGGAACATTTTTATATTAT	AAATAAGAATGTTAAAAGAGC
358	TTTTATACAATTGAAGAGC	TTCCCCAAAAATTTCT
359	TCAAGAAATAATTACGGT	ACGCAGTCCCATTTTC
360	TCTATAATGAAGGCGGTCT	CTGGCATGAGGTCTCA
361	TCTAGCGTATATGTTAGTGGA	CCTTTTTTCAATAATAGC
362	TCTACTAAACCACAGGGGG	ATCTTTAATCTTACCATCC
362d N-term	TCTACTAAACCACAGGGGG	TGCTGCTACTGCAATG
362 C-term	TCTGGTAATGAAGGAAATATCAC	ATCTTTAATCTTACCATCC
363	TCTCTCGAATTAAAAAATATTG	TAAATTCCTTTGTTGTAATA
364	TCTAACTATATGGGTATGGGC	ACCATCAGTTGTCACC
365	TCTGGAACTGCTACATATAGTAGG	TATTGACCAGTGCACG
366	TGGCTTGACATTATTTT	TTTTTTTGAATTTGTAAAAG
367	TCTAAGAAATTAAAAATATTCCC	AGAGATTATTTTTATTTTAAAT
368	TCTAAAATCATTATTCAACGT	TTTATTTTTAGTATCTAAAACG
369	TCTAGTAGAATGATTCCAGG	TTTAGAAACTCCAAGTATCTC
370	TCTACCGAATTTAATGACG	GTTAATTTGACTATTGATATATT
371	TCTAAAGATAGATATATTTTAGCAG	TAAACTCTCAAAAGCTAAAC
372	TCAGAAAAATATTCCACT	ACGTTCTTCTCTGGCT
373	TCTGAAATTGGTCAGCAAA	ACTTAAATGGAACAACC
374	TCTAAGTTCGAAAATATAATATATG	TTTGCCTAAAAAATTAGG
375	TCTGAAAAAGAAACTATTTTAAGT	GGCTTTCCTCCCTTCA
376	TCTAAAGAAAAGAAAAATTTGG	TTCATCTTTTTCAATATCA
377	TCTGGTAATAAACTGATGTATCA	GTGAGAGTGTCTTTGTTT
378	TCTGAAGATCAACTCACTATATTT	CAGATTTTTAGCTACTTGTC
379	TCTCAAATTACCCGAGAAG	TCTAGAGCGCTTTATAAG
380	TCTCTTAAAAGATTACTTACTGAAG	TTTTCTAATAGTTAGAAGCC
381	TCTCTTGGGATAGCTCACA	TTTTAAATGTGCAGAGA
382	TCTATAAAGTTTAAATTATTTTTTAA	ATTTATAATTTCCTTGGG

383	TCTATTTTACAGACGAATATACTAT	TCTATAATATCTCTCTAAAGTGA
384	TCTAGAATAATTGTTGTCGG	CCTCGCTAACATATCAC
385	TCTAATGTAAAAAAACGC	AGCTCTTACAGTCTTGC
386	TCTCTAGTATCAAAGGAGAAAGC	TTGTCTGAGTGACCAA
387	TCTGGTATGTTGTTAGCA	ATAATATGAAATATGTTGTTCA
388	TCTCTTATGATAATAAATTCATTCG	TCCGCAGAGTAAAAAA
389	TCTATGAATAGTGAACATAAAATT	TTCATAAATGTGCCAA
390	TCTAGGGAAACTTACTGGA	TTCATCTCTGCTCACC
391	TCTAAAAAAGTCATCGATTTAA	TTCTCCTTCAGCTTTTA
392	TCTATTACATATGATTTCACAAG	GTCATTTTTTCTAAAGTTTG
393	TCTAATAAATCTTGGTTGAGAA	TTTTTGTAGTTGTTTCAAT
394	TCTCCTATGTTGTCTGTTGG	TTTCATTAGATAACTATTCAGC
395	TCTACTTATCAAAAAACAGTTG	TATAGACTGAAGATAATTAATTAA
396	TTTGTCAAAGGGATTT	AAATCGATTAATCAAGTC
397	TCTAAATTATTTGATAAGTTTATAGA	TCTAAAGTAGTCCTTTAGACTA
397d	TCTAAAACTGCTACAGTTAG	TCTAAAGTAGTCCTTTAGACTA
398	TATTTAGAACAATTAAAAGAGG	TTTGTCCATAATCATTTC
399	TCTAAAGTTTTAGTAGTTGATGAT	GGTAGATATGCCTAACATT
400	TCTAAAATAGTTGAAGGCG	GTTTCCTTCCAAAAAA
401	TCTGGAATTGAATTTAAAAATG	TCCATGCTTAATAGCC
402	TCTGGAAAATATTTTGGTACAG	ATCTAAACCAATTTCTGTAC
403	TCTGAGGTTAGAATGGTAACTC	GTCCACAAAAACGTCT
404	TCTAAAATAGATGACCTAAGAAA	TAGATGTTCTACGGAGAA
405	TTGAAAATTCAGTATTATCA	AAAGATGGCAAGCCAT
406	TCTGATAAAAATAATTTAGAAGACT	TCTCTCTCCACACCATA
407	TCTAAAATTGACATGAGGAA	CTTACCTCCTGTGGCT
407d	TCTAAAATTGACATGAGGAA	CTTTTGTTGGTTACCTC
408	TCTAACCACTTACTTAACCTCA	TATTGTTAAATATGATGAAATG
409	TCTAAGGTAGTAGTAGCTATTGAT	ATGATTATACAAATTGATTAAT
409d	TCTACTGAAGAGAGAAATCCT	ATGATTATACAAATTGATTAAT
410	TCTGCTTTATTATCAGTTATTGTC	TCCCTCTTCCTTGACA
411	TCTAAAGACTATATTAACAGAATATT	AACGTTTTTGAGCTTT
412	TCTGGATTTTTTGCACAGC	TTTTGTCTTAAACGTTCT
413	TCTATTGTTGGTGAACAAGA	TTTAGATAGTCTAGCCATTT
414	TTAAATCAATATTTTCTGC	ACGGCTTGGGGCAGAG
415	TCTGAGCGAATTCCTGTTC	TACCATTATCCGTGCT
416	TCTGAAGTCATTCGTGAACA	ACTATTAAACTCCAATGTTA
417	TCAAAACAATATGATTATATC	GCGCATTGTAACAAAT
418	TCTAGCAAGCCTAATGTTG	TTTTGGTAAAAGGTCTG
419	TCTGATTTAAATAATTACATCGC	TCCTGGAAAGTTCATC
420	TCTAAACGTGAATTACTACTCG	TAGTTTATCTAAAGCGTTC
421	TCTATACGCCAGTTTTTAAG	TTTATGTATAGAAACAGCAG
422	TTTTCGAGCGATTTTG	AATGTACATAACAATAGAGAGC
423	TCTGTAACCAAAGTTGAAGAG	CAACGATCCCAAGAAC
424	TCTATGAAAGATTTTATTGAATG	GCCATTCTTACCTCCT
424d	TCTATGAAAGATTTTATTGAATG	ACGTTTTTTCTGACCG
425	TCTATAGCCTTTAATAGTTTATTT	TATAAAATAAATTTGAAGATCT
426	TCTD440ACAGTTTATAATATAAACCATG	ATCATCTTGTACCAACTC
427	TATTCTTTTGAAGAACTTTT	GCCAATAAATTCACGG
428	TCTATAAAAATTTTGATCCC	AGTCTGTTTTTTAACAAAAG
429	TCTAATCATTCCATTGAATC	TGGTTTTAGAACAACTTTA
430	TTACAAAAAAAATATCGG	AATTAAGCTGAAAATGAC
431	TCTGCGGCTCAATTAGCTG	ATTATATTCTTTTAATTTGTCA
432	TCTCGTACCTTCAAACCAG	CTTACGACGTCCTGGA
433	TCTATTAAAGCAACTTTTACTC	GTGTGTCATGACTACTGTAC
434	TCAATTTTTCAGACAACA	TGAGTAGAGCACAAGC
642	TCTAGAAAACGTAATGATACATT	GAAACGAATACGTTCTT

643	TCTGATTGTCAAATTACACCA	ACTACCTACCGTTTTCAC
644	TCTATTTTTCGTGGTGATAA	TTTGATGGTAACAGTCG
645	TTTTTTAATATTGAATATCAC	AGAAAGGCGCTCTTCT
646	TCTAAGGGAGTCCAATATATG	TATCTTTAATAAAGCCCTA
647	TCTCGTCGCATGAATACCA	CATCCCATAAATTTGTT
648	TCTATAGAATTTTCAGGGC	CAAGACATTTCTTAAAGC
649	TCTGCTACTCACTCTAACTCAG	TTTTGTTTTAGCGATG
650	TGCTCTTCTTCAAATACT	TTTTAAACCATGCTGT
651	TCTCTAACACCATTTACAAAAG	TTTGTAAAGACCTTCTTT
652	TCTCAACAAGGTATTATGGATA	TTCCTCGTTTATTAATTT
653	TCTAAAATTTTAGGTACACCA	AAAGAAAAGATGTGCC
654	TCTGGAAAAATGGTTAAGAA	CTGTGCAGGCTCAAAT
655	TCTAAATTCGTCCGAACCGT	AATTGTCCAGTCTAAGTTA
656	TCTGGTCTTCCAACGCAGC	ATTTAGTGTTATTTCTCCTG
657	TGCTCAGGTAAAACAT	TTTTTTAAGTGATGATGAA
658	TCTGAAAGCAAATCTTTGC	CTTTGTCTGCTTCACTT
659	TGTGCTAATTGGATTG	TTTTGGGGTTACTTTAC
660	TGTGGAAATGTCGGAG	TTTTGCTGAAATAATGTT
661	TGTCAGTCAAACCACA	ATCATACGAATGCAAC
662	TCTGCTAGTTTTTATTTTTTCC	TTTTTCATATTTTTTCAAA
663	TGTGGAAGTAAATCAGC	ATTATTTTTATAAGCATGTG
664	TCTGTTAAATTAAAATCGTTACTG	GAGTTGTCTTTTTTTGTC
665	TCTATTGCTGGTCCTAGTG	GATAAGCACTTTCCTTAA
666	TTATTTTTTGGAAATTGG	GCCTAAAAACCAATCA
667	TCTGCTGTATTTACACTCGTC	ATGTTTATGGCTTGCT
668	TTTTATATGAAAGAACAACA	TTGTATCTTCTCCTGACC
669	TCAATTATTATTGGGTTAA	ATATACCCTAGACTTTTTGA
670	TCTCCTAAATTAACCCTAGTCT	GGCTTTAAAGTTCGATA
671	TCTAGTCTTGCGAAGGCAG	TTTATCGTAAGCACTTAGG
672	TCTGTATTTACACTCGTCTTACA	ATGTTTATGGCTTGCTT
673	TCTGGAGGATTTTATATGAAAG	TTGTATCTTCTCCTGACC
674	TCTGTTAAATTAAAATCGTTACTG	GAGTTGTCTTTTTTTGTCT
675	TCTGGTTCATCAGACAAACA	TTCAACTTGATTGCCA
676	TCTGTAGTTAAAGTTGGTATTAACG	TTTTGCAATTTTTGC
677	TCTGTATTAGAAGTACATGCTGA	TTTTAATGCTGTTTGAA
678	TCTGAGACACCAGTAATGGC	TTTTTTAGCTAAGGCTG
679	TCTGCTAACAAGCAGGATC	TTTTGCTAAACCTTCTG
680	TCTAATAAGTCCAGTAACTCTAAG	ATTCATATTAACACGATGC
681	TCTGCTTTTGATGTAATTATGC	TTTGCGTTTTGGAGGG
682	TCTATTAACTATGAGGTTAAAGC	TGCACCTTGATGGCGA
683	TCTGTAATTGTTGAACTTAGTTTG	CCATAATATTTGATGCTG
684	TCTCTTAGGAAGTATAAGCAAA	TTCTAATCCTACAGCATG
685	TCTAAAATTTGTCTGGTTGG	AAAAATTCCTCCTAAATTAA
686	TCTGACTTTTATGATATCAATCTT	AAAGTTTTGACTATTACTGATAG
687	TATGCTATTATGCAAAAAG	TGGGGGAGATAGTTATG
688	TCTGCAATCGTTTCAGCAG	TTGACAGAAAGCTAATTG

TABLE III – RESULTS FOR *in vivo* GBS CHALLENGE

GBS #	% survival	
	Pre-immune	Post-immune
1	18.7	22.2
4gst	19.4	37.2
4his	25.0	75.0
8	14.3	42.1
10	29.1	36.0
15	30.0	60.9

GBS #	% survival	
	Pre-immune	Post-immune
110	11.1	30.0
113	17.6	29.4
114	40.0	52.2
117	27.8	36.8
119	36.4	52.2
139	23.1	26.7

16	33.3	53.8
18	29.4	50.0
21	5.9	10.0
22	36.8	63.1
24	38.5	41.4
25	28.6	85.7
32	20.0	25.0
35	0.0	17.6
45	26.7	37.5
48	20.0	25.0
52	14.2	17.3
53	23.8	29.2
54	22.7	44.0
55	50.0	52.9
57	33.3	55.6
58	6.7	11.8
62	15.8	36.4
63	21.4	42.9
65	3.7	23.3
67	23.5	27.8
71	13.3	26.7
73	28.6	39.1
80	38.8	56.5
84	33.3	37.5
85	30.8	62.5
90	14.3	22.7
94	25.0	30.0
95	16.7	23.1
98	5.9	11.1
100	26.9	42.9
103	16.7	52.9
106	10.0	18.2

150	21.6	44.4
153	25.0	30.0
155	22.6	36.8
157	14.3	31.8
158	22.6	40.0
163	29.6	37.9
164	25.0	43.8
173	17.9	38.7
176	20.0	38.9
177	21.7	33.3
181	5.0	21.7
186	41.2	52.6
188	11.8	23.5
189	21.4	31.6
195	32.1	64.7
206	33.3	50.0
211	30.8	33.3
232	50.0	57.1
233	34.8	55.2
236	57.1	70.6
243	46.7	52.9
263	15.4	35.7
273	61.5	75.0
276	23.8	44.4
296	25.0	28.6
297	13.3	23.5
298	20.0	22.2
302	30.0	52.2
304	33.3	40.9
305	42.1	70.0
316	38.5	42.9
318	7.1	15.8

TABLE IV – COMPARISON OF GBS*nnn* NUMBERING AND SEQ ID NUMBER

GBS numbering	Sequence listing
GBS1	SEQ ID 3532 & 8736
GBS2	SEQ ID 4530 & 8818
GBS3	SEQ ID 6266 & 8958
GBS4	SEQ ID 2 & 8786
GBS5	SEQ ID 2598 & 8674
GBS6	SEQ ID 398 & 8496
GBS7	SEQ ID 8790 & 9798
GBS8	SEQ ID 8694
GBS9	SEQ ID 4540 & 8822
GBS10	SEQ ID 8718
GBS11	SEQ ID 5884 & 8930
GBS12	SEQ ID 8764 & 9692
GBS13	SEQ ID 8484
GBS14	SEQ ID 5406 & 8892
GBS15	SEQ ID 4 & 8710
GBS16	SEQ ID 944 & 8538
GBS17	SEQ ID 1770 & 8602
GBS18	SEQ ID 6860 & 9002
GBS19	SEQ ID 4422 & 8812
GBS20	SEQ ID 308 & 8488
GBS21	SEQ ID 8762

GBS numbering	Sequence listing
GBS345	SEQ ID 2442
GBS346	SEQ ID 2768
GBS347	SEQ ID 2766
GBS348	SEQ ID 8658
GBS349	SEQ ID 2360
GBS350	SEQ ID 8698
GBS351	SEQ ID 2970
GBS352	SEQ ID 8692
GBS353	SEQ ID 3454
GBS354	SEQ ID 8754
GBS355	SEQ ID 8752
GBS356	SEQ ID 8724
GBS357	SEQ ID 8720
GBS358	SEQ ID 3184
GBS359	SEQ ID 3948
GBS360	SEQ ID 3926
GBS361	SEQ ID 8770
GBS362	SEQ ID 8768
GBS363	SEQ ID 3816
GBS364	SEQ ID 1452
GBS365	SEQ ID 1398

GBS22	SEQ ID 8584
GBS23	SEQ ID 8512
GBS24	SEQ ID 1694 & 8598
GBS25	SEQ ID 3180 & 8714
GBS26	SEQ ID 8820
GBS27	SEQ ID 8774
GBS28	SEQ ID 8738
GBS29	SEQ ID 8744
GBS30	SEQ ID 8860
GBS31	SEQ ID 8702
GBS32	SEQ ID 8910 & 10142
GBS33	SEQ ID 5734 & 8912
GBS34	SEQ ID 5750 & 8916
GBS35	SEQ ID 8908
GBS36	SEQ ID 8542
GBS37	SEQ ID 8564
GBS38	SEQ ID 2122 & 8642
GBS39	SEQ ID 8480
GBS40	SEQ ID 8654
GBS41	SEQ ID 1176 & 8562
GBS42	SEQ ID 4856 & 8850
GBS43	SEQ ID 672 & 8520
GBS44	SEQ ID 9000
GBS45	SEQ ID 9018
GBS46	SEQ ID 1834 & 8608
GBS47	SEQ ID 8588
GBS48	SEQ ID 8594 & 8596
GBS49	SEQ ID 8494 & 9490
GBS50	SEQ ID 1236 & 8566
GBS51	SEQ ID 5410
GBS52	SEQ ID 3920
GBS53	SEQ ID 8586
GBS54	SEQ ID 3442
GBS55	SEQ ID 9020 & 10338
GBS56	SEQ ID 2510 & 8668
GBS57	SEQ ID 8854
GBS58	SEQ ID 8664
GBS59	SEQ ID 3744
GBS60	SEQ ID 8760
GBS61	SEQ ID 8776
GBS62	SEQ ID 2244
GBS63	SEQ ID 390
GBS64	SEQ ID 374
GBS65	SEQ ID 8544
GBS66	SEQ ID 3028
GBS67	SEQ ID 3746
GBS68	SEQ ID 4012
GBS69	SEQ ID 4916
GBS70	SEQ ID 3718
GBS71	SEQ ID 8906
GBS72	SEQ ID 1348
GBS73	SEQ ID 220
GBS74	SEQ ID 5872
GBS75	SEQ ID 8926
GBS76	SEQ ID 5862
GBS77	SEQ ID 3256
GBS78	SEQ ID 3262
GBS79	SEQ ID 3264
GBS80	SEQ ID 8780

GBS366	SEQ ID 8574
GBS367	SEQ ID 1340
GBS368	SEQ ID 1598
GBS369	SEQ ID 4822
GBS370	SEQ ID 8844
GBS371	SEQ ID 4926
GBS372	SEQ ID 4956
GBS373	SEQ ID 5062
GBS374	SEQ ID 8878
GBS375	SEQ ID 326
GBS376	SEQ ID 5380
GBS377	SEQ ID 5468
GBS378	SEQ ID 5570
GBS379	SEQ ID 8918
GBS380	SEQ ID 156
GBS381	SEQ ID 8934
GBS382	SEQ ID 8610
GBS383	SEQ ID 4738
GBS384	SEQ ID 8836
GBS385	SEQ ID 1094
GBS386	SEQ ID 9038
GBS387	SEQ ID 8558
GBS388	SEQ ID 9040
GBS389	SEQ ID 8516
GBS390	SEQ ID 8952
GBS391	SEQ ID 8522
GBS392	SEQ ID 6220
GBS393	SEQ ID 8966
GBS394	SEQ ID 8960
GBS395	SEQ ID 6276
GBS396	SEQ ID 8468
GBS397	SEQ ID 6262
GBS398	SEQ ID 8806
GBS399	SEQ ID 1960
GBS400	SEQ ID 3154
GBS401	SEQ ID 3170
GBS402	SEQ ID 4236
GBS403	SEQ ID 8798
GBS404	SEQ ID 8800
GBS405	SEQ ID 8508
GBS406	SEQ ID 8506
GBS407	SEQ ID 6484
GBS408	SEQ ID 9042
GBS409	SEQ ID 6678
GBS410	SEQ ID 4064
GBS411	SEQ ID 9044
GBS412	SEQ ID 9046
GBS413	SEQ ID 272
GBS414	SEQ ID 8946
GBS415	SEQ ID 8944
GBS416	SEQ ID 6044
GBS417	SEQ ID 1874
GBS418	SEQ ID 5146
GBS419	SEQ ID 2638
GBS420	SEQ ID 2104
GBS421	SEQ ID 2108
GBS422	SEQ ID 714
GBS423	SEQ ID 6884
GBS424	SEQ ID 4874

GBS81	SEQ ID 2706
GBS82	SEQ ID 2898
GBS83	SEQ ID 8772
GBS84	SEQ ID 4182
GBS85	SEQ ID 216
GBS86	SEQ ID 2978
GBS87	SEQ ID 3452
GBS88	SEQ ID 5694
GBS89	SEQ ID 2682
GBS90	SEQ ID 8476
GBS91	SEQ ID 8938
GBS92	SEQ ID 8964 & 10238
GBS93	SEQ ID 2848
GBS94	SEQ ID 1592
GBS95	SEQ ID 2224
GBS96	SEQ ID 2130
GBS97	SEQ ID 800
GBS98	SEQ ID 8746
GBS99	SEQ ID 4240
GBS100	SEQ ID 8782
GBS101	SEQ ID 6902
GBS102	SEQ ID 6894
GBS103	SEQ ID 6
GBS104	SEQ ID 8778
GBS105	SEQ ID 1400
GBS106	SEQ ID 8502
GBS107	SEQ ID 6026
GBS108	SEQ ID 8532
GBS109	SEQ ID 4116
GBS110	SEQ ID 6832
GBS111	SEQ ID 8842
GBS112	SEQ ID 8904
GBS113	SEQ ID 300
GBS114	SEQ ID 8968
GBS115	SEQ ID 5164
GBS116	SEQ ID 5152
GBS117	SEQ ID 8962
GBS118	SEQ ID 2508
GBS119	SEQ ID 8814
GBS120	SEQ ID 8874
GBS121	SEQ ID 3826
GBS122	SEQ ID 9006
GBS123	SEQ ID 6310
GBS124	SEQ ID 260
GBS125	SEQ ID 3872
GBS126	SEQ ID 6736
GBS127	SEQ ID 8816
GBS128	SEQ ID 752
GBS129	SEQ ID 8990
GBS130	SEQ ID 9004
GBS131	SEQ ID 6198
GBS132	SEQ ID 8730
GBS133	SEQ ID 474
GBS134	SEQ ID 9008
GBS135	SEQ ID 8882
GBS136	SEQ ID 1188
GBS137	SEQ ID 3960
GBS138	SEQ ID 9052
GBS139	SEQ ID 884

GBS425	SEQ ID 3978
GBS426	SEQ ID 3976
GBS427	SEQ ID 6958
GBS428	SEQ ID 3398
GBS429	SEQ ID 3402
GBS430	SEQ ID 8840
GBS431	SEQ ID 8902
GBS432	SEQ ID 8534
GBS433	SEQ ID 2558
GBS434	SEQ ID 8590
GBS435	SEQ ID 484
GBS436	SEQ ID 8472
GBS437	SEQ ID 466
GBS438	SEQ ID 362
GBS439	SEQ ID 900
GBS440	SEQ ID 8536
GBS441	SEQ ID 936
GBS442	SEQ ID 940
GBS443	SEQ ID 998
GBS444	SEQ ID 1776
GBS445	SEQ ID 8634
GBS446	SEQ ID 2048
GBS447	SEQ ID 1654
GBS448	SEQ ID 8592
GBS449	SEQ ID 1634
GBS450	SEQ ID 1630
GBS451	SEQ ID 2098
GBS452	SEQ ID 2062
GBS453	SEQ ID 8636
GBS454	SEQ ID 1734
GBS455	SEQ ID 1690
GBS456	SEQ ID 1684
GBS457	SEQ ID 8656
GBS458	SEQ ID 8650
GBS459	SEQ ID 2152
GBS460	SEQ ID 2148
GBS461	SEQ ID 2394
GBS462	SEQ ID 2778
GBS463	SEQ ID 8688
GBS464	SEQ ID 8684
GBS465	SEQ ID 8682
GBS466	SEQ ID 2694
GBS467	SEQ ID 2350
GBS468	SEQ ID 8660
GBS469	SEQ ID 2998
GBS470	SEQ ID 2988
GBS471	SEQ ID 2924
GBS472	SEQ ID 2910
GBS473	SEQ ID 2882
GBS474	SEQ ID 2878
GBS475	SEQ ID 2856
GBS476	SEQ ID 8690
GBS477	SEQ ID 3112
GBS478	SEQ ID 3432
GBS479	SEQ ID 3460
GBS480	SEQ ID 3504
GBS481	SEQ ID 8734
GBS482	SEQ ID 8740
GBS483	SEQ ID 3606

GBS140	SEQ ID 8632
GBS141	SEQ ID 1768
GBS142	SEQ ID 8600
GBS143	SEQ ID 9054
GBS144	SEQ ID 2238
GBS145	SEQ ID 8700
GBS146	SEQ ID 8696
GBS147	SEQ ID 8526
GBS148	SEQ ID 9010
GBS149	SEQ ID 8732
GBS150	SEQ ID 3736
GBS151	SEQ ID 3188
GBS152	SEQ ID 3952
GBS153	SEQ ID 3904
GBS154	SEQ ID 4024
GBS155	SEQ ID 8796
GBS156	SEQ ID 4646
GBS157	SEQ ID 4812
GBS158	SEQ ID 5504
GBS159	SEQ ID 8628
GBS160	SEQ ID 8924
GBS161	SEQ ID 8922
GBS162	SEQ ID 168
GBS163	SEQ ID 224
GBS164	SEQ ID 1102
GBS165	SEQ ID 3672
GBS166	SEQ ID 8712
GBS167	SEQ ID 4214
GBS168	SEQ ID 9016
GBS169	SEQ ID 4346
GBS170	SEQ ID 8982
GBS171	SEQ ID 6720
GBS172	SEQ ID 6704
GBS173	SEQ ID 8788
GBS174	SEQ ID 6150
GBS175	SEQ ID 62
GBS176	SEQ ID 8478
GBS177	SEQ ID 8876
GBS178	SEQ ID 6078
GBS179	SEQ ID 8848
GBS180	SEQ ID 3062
GBS181	SEQ ID 1924
GBS182	SEQ ID 3774
GBS183	SEQ ID 4796
GBS184	SEQ ID 1978
GBS185	SEQ ID 1046
GBS186	SEQ ID 8470
GBS187	SEQ ID 844
GBS188	SEQ ID 3410
GBS189	SEQ ID 6986
GBS190	SEQ ID 8842
GBS191	SEQ ID 1814
GBS192	SEQ ID 8618
GBS193	SEQ ID 2382
GBS194	SEQ ID 3912
GBS195	SEQ ID 8
GBS196	SEQ ID 4944
GBS197	SEQ ID 5486
GBS198	SEQ ID 8896

GBS484	SEQ ID 3562
GBS485	SEQ ID 3552
GBS486	SEQ ID 3762
GBS487	SEQ ID 3756
GBS488	SEQ ID 3732
GBS489	SEQ ID 3730
GBS490	SEQ ID 3704
GBS491	SEQ ID 3698
GBS492	SEQ ID 3252
GBS493	SEQ ID 3244
GBS494	SEQ ID 3238
GBS495	SEQ ID 8722
GBS496	SEQ ID 8716
GBS497	SEQ ID 3876
GBS498	SEQ ID 3858
GBS499	SEQ ID 8758
GBS500	SEQ ID 4022
GBS501	SEQ ID 4106
GBS502	SEQ ID 1406
GBS503	SEQ ID 8580
GBS504	SEQ ID 4578
GBS505	SEQ ID 4566
GBS506	SEQ ID 8832
GBS507	SEQ ID 8830
GBS508	SEQ ID 4644
GBS509	SEQ ID 8828
GBS510	SEQ ID 8826
GBS511	SEQ ID 4892
GBS512	SEQ ID 4970
GBS513	SEQ ID 4974
GBS514	SEQ ID 8862
GBS515	SEQ ID 8864
GBS516	SEQ ID 8866
GBS517	SEQ ID 8868
GBS518	SEQ ID 9012
GBS519	SEQ ID 5068
GBS520	SEQ ID 8870
GBS521	SEQ ID 5228
GBS522	SEQ ID 322
GBS523	SEQ ID 8492
GBS524	SEQ ID 8894
GBS525	SEQ ID 5430
GBS526	SEQ ID 5414
GBS527	SEQ ID 5524
GBS528	SEQ ID 8898
GBS529	SEQ ID 5670
GBS530	SEQ ID 5630
GBS531	SEQ ID 5588
GBS532	SEQ ID 1324
GBS533	SEQ ID 8914
GBS534	SEQ ID 8550
GBS535	SEQ ID 8568
GBS536	SEQ ID 1288
GBS537	SEQ ID 5798
GBS538	SEQ ID 8920
GBS539	SEQ ID 158
GBS540	SEQ ID 8482
GBS541	SEQ ID 184
GBS542	SEQ ID 9048

GBS199	SEQ ID 1162
GBS200	SEQ ID 8936
GBS201	SEQ ID 4550
GBS202	SEQ ID 8666
GBS203	SEQ ID 6478
GBS204	SEQ ID 1996
GBS205	SEQ ID 18
GBS206	SEQ ID 8552
GBS207	SEQ ID 3822
GBS208	SEQ ID 3916
GBS209	SEQ ID 3918
GBS210	SEQ ID 3738
GBS211	SEQ ID 4680
GBS212	SEQ ID 8750
GBS213	SEQ ID 8500
GBS214	SEQ ID 8498
GBS215	SEQ ID 9022
GBS216	SEQ ID 8606
GBS217	SEQ ID 9024
GBS218	SEQ ID 8652
GBS219	SEQ ID 8646
GBS220	SEQ ID 2730
GBS221	SEQ ID 9028
GBS222	SEQ ID 3842
GBS223	SEQ ID 8794
GBS224	SEQ ID 9026
GBS225	SEQ ID 8834
GBS226	SEQ ID 4966
GBS227	SEQ ID 5030
GBS228	SEQ ID 5050
GBS229	SEQ ID 9056
GBS230	SEQ ID 1296
GBS231	SEQ ID 5810
GBS232	SEQ ID 5830
GBS233	SEQ ID 4722
GBS234	SEQ ID 1106
GBS235	SEQ ID 8560
GBS236	SEQ ID 6162
GBS237	SEQ ID 8706
GBS238	SEQ ID 4246
GBS239	SEQ ID 8980
GBS240	SEQ ID 8986
GBS241	SEQ ID 9030
GBS242	SEQ ID 9032
GBS243	SEQ ID 8678
GBS244	SEQ ID 6554
GBS245	SEQ ID 8994
GBS246	SEQ ID 6864
GBS247	SEQ ID 8856
GBS248	SEQ ID 454
GBS249	SEQ ID 8620
GBS250	SEQ ID 8634
GBS251	SEQ ID 2258
GBS252	SEQ ID 8648
GBS253	SEQ ID 2526
GBS254	SEQ ID 2710
GBS255	SEQ ID 2966
GBS256	SEQ ID 3424
GBS257	SEQ ID 3550

GBS543	SEQ ID 8932
GBS544	SEQ ID 5880
GBS545	SEQ ID 44
GBS546	SEQ ID 9014
GBS547	SEQ ID 12
GBS548	SEQ ID 8614
GBS549	SEQ ID 8612
GBS550	SEQ ID 4720
GBS551	SEQ ID 4710
GBS552	SEQ ID 1086
GBS553	SEQ ID 1088
GBS554	SEQ ID 1138
GBS555	SEQ ID 8748
GBS556	SEQ ID 5968
GBS557	SEQ ID 774
GBS558	SEQ ID 1192
GBS559	SEQ ID 1196
GBS560	SEQ ID 1268
GBS561	SEQ ID 8518
GBS562	SEQ ID 8676
GBS563	SEQ ID 2296
GBS564	SEQ ID 2300
GBS565	SEQ ID 8950
GBS566	SEQ ID 694
GBS567	SEQ ID 680
GBS568	SEQ ID 6300
GBS569	SEQ ID 8956
GBS570	SEQ ID 8972
GBS571	SEQ ID 8970
GBS572	SEQ ID 3300
GBS573	SEQ ID 3304
GBS574	SEQ ID 8726
GBS575	SEQ ID 8810
GBS576	SEQ ID 4418
GBS577	SEQ ID 8808
GBS578	SEQ ID 4382
GBS579	SEQ ID 4378
GBS580	SEQ ID 1932
GBS581	SEQ ID 8622
GBS582	SEQ ID 8624
GBS583	SEQ ID 1962
GBS584	SEQ ID 8708
GBS585	SEQ ID 8672
GBS586	SEQ ID 6444
GBS587	SEQ ID 8976
GBS588	SEQ ID 8804
GBS589	SEQ ID 8514
GBS590	SEQ ID 8510
GBS591	SEQ ID 630
GBS592	SEQ ID 8504
GBS593	SEQ ID 514
GBS594	SEQ ID 8978
GBS595	SEQ ID 6738
GBS596	SEQ ID 6712
GBS597	SEQ ID 6686
GBS598	SEQ ID 6674
GBS599	SEQ ID 6662
GBS600	SEQ ID 8988
GBS601	SEQ ID 8578

GBS258	SEQ ID 3752
GBS259	SEQ ID 8756
GBS260	SEQ ID 4162
GBS261	SEQ ID 1530
GBS262	SEQ ID 8572
GBS263	SEQ ID 1616
GBS264	SEQ ID 8824
GBS265	SEQ ID 4554
GBS266	SEQ ID 4652
GBS267	SEQ ID 4980
GBS268	SEQ ID 5038
GBS269	SEQ ID 5534
GBS270	SEQ ID 1998
GBS271	SEQ ID 8570
GBS272	SEQ ID 22
GBS273	SEQ ID 5994
GBS274	SEQ ID 774
GBS275	SEQ ID 2308
GBS276	SEQ ID 8942
GBS277	SEQ ID 8954
GBS278	SEQ ID 8524
GBS279	SEQ ID 6292
GBS280	SEQ ID 6254
GBS281	SEQ ID 4458
GBS282	SEQ ID 4444
GBS283	SEQ ID 9034
GBS284	SEQ ID 6456 & 8974
GBS285	SEQ ID 8802
GBS286	SEQ ID 9036
GBS287	SEQ ID 5354
GBS288	SEQ ID 5374
GBS289	SEQ ID 8616
GBS290	SEQ ID 8680
GBS291	SEQ ID 8530
GBS292	SEQ ID 8998
GBS293	SEQ ID 8582
GBS294	SEQ ID 8604
GBS295	SEQ ID 2722
GBS296	SEQ ID 2658
GBS297	SEQ ID 3024
GBS298	SEQ ID 8704
GBS299	SEQ ID 3268
GBS300	SEQ ID 4170
GBS301	SEQ ID 8576
GBS302	SEQ ID 8670
GBS303	SEQ ID 8554
GBS304	SEQ ID 5846
GBS305	SEQ ID 208
GBS306	SEQ ID 212
GBS307	SEQ ID 8992
GBS308	SEQ ID 8880
GBS309	SEQ ID 3386
GBS310	SEQ ID 286
GBS311	SEQ ID 3964
GBS312	SEQ ID 4660
GBS313	SEQ ID 4090
GBS314	SEQ ID 8556
GBS315	SEQ ID 1766
GBS316	SEQ ID 2000

GBS602	SEQ ID 8948
GBS603	SEQ ID 6132
GBS604	SEQ ID 5282
GBS605	SEQ ID 5302
GBS606	SEQ ID 8884
GBS607	SEQ ID 5314
GBS608	SEQ ID 8886
GBS609	SEQ ID 8888
GBS610	SEQ ID 8890
GBS611	SEQ ID 6028
GBS612	SEQ ID 8474
GBS613	SEQ ID 5092
GBS614	SEQ ID 8872
GBS615	SEQ ID 6052
GBS616	SEQ ID 8940
GBS617	SEQ ID 1824
GBS618	SEQ ID 6600
GBS619	SEQ ID 6608
GBS620	SEQ ID 6620
GBS621	SEQ ID 864
GBS622	SEQ ID 8640
GBS623	SEQ ID 8996
GBS624	SEQ ID 9050
GBS625	SEQ ID 2812
GBS626	SEQ ID 8858
GBS627	SEQ ID 8852
GBS628	SEQ ID 8784
GBS629	SEQ ID 6950
GBS630	SEQ ID 4502
GBS631	SEQ ID 4492
GBS632	SEQ ID 4488
GBS633	SEQ ID 8728
GBS634	SEQ ID 3066
GBS635	SEQ ID 8838
GBS636	SEQ ID 4772
GBS637	SEQ ID 8626
GBS638	SEQ ID 8984
GBS639	SEQ ID 8546
GBS640	SEQ ID 6780
GBS641	SEQ ID 900
GBS642	1312
GBS643	1772
GBS644	1956
GBS645	2726
GBS646	3348
GBS647	3770
GBS648	4934
GBS649	5076
GBS650	5446
GBS651	5602
GBS652	5610
GBS653	5760
GBS654	6096
GBS655	6656
GBS656	9324
GBS657	10782
GBS658	8802
GBS659	9344
GBS660	9410

GBS317	SEQ ID 4210
GBS318	SEQ ID 8548
GBS319	SEQ ID 892
GBS320	SEQ ID 916
GBS321	SEQ ID 8846
GBS322	SEQ ID 8540
GBS323	SEQ ID 2102
GBS324	SEQ ID 8490
GBS325	SEQ ID 8900
GBS326	SEQ ID 8630
GBS327	SEQ ID 5856
GBS328	SEQ ID 6016
GBS329	SEQ ID 8928
GBS330	SEQ ID 8792
GBS331	SEQ ID 922
GBS332	SEQ ID 1004
GBS333	SEQ ID 1786
GBS334	SEQ ID 1784
GBS335	SEQ ID 1782
GBS336	SEQ ID 1886
GBS337	SEQ ID 2010
GBS338	SEQ ID 8638
GBS339	SEQ ID 2080
GBS340	SEQ ID 8594 & 8596
GBS341	SEQ ID 2280
GBS342	SEQ ID 2266
GBS343	SEQ ID 8644
GBS344	SEQ ID 8662

GBS661	9428
GBS662	9286
GBS663	9294
GBS664	9034
GBS665	10546
GBS666	10610
GBS667	9052
GBS668	9036
GBS669	9010
GBS670	10730
GBS671	9020
GBS672	9052
GBS673	9036
GBS674	9034
GBS675	10634
GBS676	10692
GBS677	10746
GBS678	9330
GBS679	9404
GBS680	6668
GBS681	4264
GBS682	6762
GBS683	9290
GBS684	9614
GBS685	10454
GBS686	2774
GBS687	4620
GBS688	10224

TABLE V – NUCLEOTIDES DELETED IN EXPRESSION OF GBS*nnn* PROTEINS

GBS	Deleted nucleotides
11d	1-153
31d	1-129
64d	1-165
68d	2029-2796
70d	1-402
74d	1-975
79d	1-201
105dN	2689-4119
105dC	1-2688
105d	1-2688
109d	1-120
130d	1-518
170d	1-111
182d	1596-1674
195C	1-1710
195N	1711-3243
209d	757-912
210d	1-99 & 777-879
220d	1-120
231d	1-54
235d	1-270
246d	1-75
248d	1-591

GBS	Deleted nucleotides
272d	1-531
277d	1-318
281d	1-54
287d	1-108
288d	1-72
293C	1-1229
293N	1230-2379
317N	1729-4107
317C	1-2379
326N	1707-2652
326dN	2326-3927
327N	3034-6831
327C	1-3033
333d	1-150
339d	1-111
352d	1-158
362N	1707-2652
362C	1-1706
397d	1-348
399d	1-111
407d	1174-1473
409d	1-297
424d	1327-1671

TABLE VI – PREDICTED FUNCTIONS FOR CERTAIN SEQ IDs

SEQ ID	Function
6	manganese ABC transporter, ATP-binding protein (psaB)
12	iron (chelated) ABC transporter, permease protein (psaC)
18	peptidyl-prolyl cis-trans isomerase, cyclophilin-type
26	chorismate binding enzyme (pabB)
30	probable transposase (insertion sequence IS861)
42	peptidase, M20/M25/M40 family
44	drug transporter
50	ribosomal protein L11 (rplK)
54	ribosomal protein L1 (rplA)
62	peptide ABC transporter, permease protein
66	peptide ABC transporter, permease protein
78	uridylate kinase (pyrH)
84	ribosome recycling factor (frr)
104	PhoH family protein (phoH)
110	MutT/nudix family protein superfamily
116	tetracenomycin polyketide synthesis O-methyltransferase TcmP
134	phosphopantetheine adenylyltransferase (coaD)
140	PDZ domain protein
144	5-nucleotidase family protein
156	VanZF-related protein
158	ABC transporter, ATP-binding/permease protein
162	ABC transporter, ATP-binding/permease protein
168	BioY family protein
180	acetyl-CoA acetyltransferase
188	endonuclease III (nth)
196	glucokinase (gki)
200	rhodanese family protein
204	elongation factor Tu family protein (typA)
212	UDP-N-acetylglucosamine--N-acetylmuramyl-(pentapeptide) pyrophosphoryl-
216	cell division protein DivIB
220	cell division protein FtsA (ftsA)
224	cell division protein FtsZ (ftsZ)
236	ylmH protein (ylmH)
240	cell division protein DivIVA (divIVA)
244	isoleucyl-tRNA synthetase (ileS)
252	MutT/nudix family protein
256	ATP-dependent Clp protease, ATP-binding subunit ClpE (clpE)
268	methylenetetrahydrofolate dehydrogenase/methenyltetrahydrofolate cycloh
274	exodeoxyribonuclease VII, large subunit (xseA)
278	exodeoxyribonuclease VII, small subunit (xseB)
282	geranyltranstransferase (ispA)
286	hemolysin A
290	transcriptional repressor
296	DNA repair protein RecN (recN)
300	degV family protein (degV)
322	peptide ABC transporter, permease protein (oppC)
326	peptide ABC transporter, ATP-binding protein (oppD)
328	peptide ABC transporter, ATP-binding protein (oppF)
348	4-diphosphocytidyl-2C-methyl-D-erythritol kinase (ispE)
352	adc operon repressor AdcR (adcR)
356	zinc ABC transporter, ATP-binding protein (adcC)
370	tyrosyl-tRNA synthetase (tyrS)
374	penicillin-binding protein 1B (pbp1B)
378	DNA-directed RNA polymerase, beta subunit (rpoB)
382	dna-directed rna polymerase beta' chain

390	competence protein CglA (cglA)
406	acetate kinase (ackA)
410	transcriptional regulator
418	pyrroline-5-carboxylate reductase (proC)
422	glutamyl-aminopeptidase (pepA)
432	thioredoxin family protein
436	tRNA binding domain protein (pheT)
440	methyltransferase
442	single-strand DNA-binding protein, authentic point mutation (ssbB)
454	GAF domain protein (lytS)
466	lrgB protein (lrgB)
474	oligopeptide ABC transporter, permease protein
476	peptide ABC transporter, ATP-binding protein
480	peptide ABC transporter, ATP-binding protein (oppF)
484	PTS system, IIABC components (treB)
488	alpha amylase family protein (treC)
494	transcriptional regulator, BglG family
506	transcriptional regulator, BglG family
508	PTS system, IIB component
514	PTS system, IIC component
518	transketolase, N-terminal subunit (tktA)
528	ribosomal protein S15 (rpsO)
546	cysteinyl-tRNA synthetase (cysS)
554	RNA methyltransferase, TrmH family, group 3
562	DegV family protein (degV)
572	ribosomal protein S9 (rpsI)
576	integrase, phage family
580	transcriptional regulator
596	recombination protein
626	transcriptional regulator MutR
630	transporter
640	amino acid ABC transporter, permease protein (opuBB)
642	glycine betaine/L-proline transport ATP binding subunit (proV)
654	lectin, alpha subunit precursor
662	transcriptional regulator
664	acetyltransferase, GNAT family
666	acetyltransferase, GNAT family (rimJ)
670	acetyltransferase, GNAT family
676	transcriptional regulator, tetR family domain protein
680	ABC transporter efflux protein, DrrB family
690	IS1381, transposase OrfA/OrfB, truncation
714	magnesium transporter, CorA family
718	oxidoreductase, Gfo/Idh/MocA family
722	valyl-tRNA synthetase (valS)
730	acetyltransferase, GNAT family
746	methyltransferase
750	bacteriophage L54a, integrase
754	DNA-damage-inducible protein J
774	cation efflux system protein
778	oxidoreductase, aldo/keto reductase family
784	alcohol dehydrogenase, zinc-containing
790	3-oxoadipate enol-lactone hydrolase/4-carboxymuconolactone decarboxylas
804	ribonucleoside-diphosphate reductase, alpha subunit (nrdE)
808	nrdI protein (nrdI)
812	Ribonucleotide reductases
824	elaA protein (elaA)
828	RNA methyltransferase, TrmA family
832	RecX family protein
840	-identity (jag)

844	membrane protein, 60 kDa (yidC)
856	UTP-glucose-1-phosphate uridylyltransferase (galU)
864	rhomboid family protein
884	MORN motif family
892	transcriptional regulator
896	adenylosuccinate lyase (purB)
908	phosphoribosylaminoimidazole carboxylase, catalytic subunit (purE)
912	phosphoribosylamine--glycine ligase (purD)
916	phosphosugar-binding transcriptional regulator
920	acetyl xylan esterase
922	ROK family protein (gki)
926	N-acetylneuraminate lyase (nanA)
936	sugar ABC transporter, permease protein
940	sugar ABC transporter, permease protein (msmF)
952	LysM domain protein, authentic frameshift
956	zoocin A endopeptidase
958	phosphoribosylaminoimidazolecarboxamide formyltransferase/IMP cyclohydr
962	acetyltransferase, GNAT family family
964	phosphoribosylglycinamide formyltransferase (purN)
968	phosphoribosylformylglycinamidine cyclo-ligase (purM)
972	amidophosphoribosyltransferase (purF)
980	phosphoribosylformylglycinamidine synthase
984	phosphoribosylaminoimidazole-succinocarboxamide synthase (purC)
1042	oligoendopeptidase F (pepF)
1060	ebsC protein
1068	hydrolase, haloacid dehalogenase-like family
1076	riboflavin synthase, beta subunit (ribH)
1082	riboflavin biosynthesis protein RibD (ribD)
1086	Mn2+/Fe2+ transporter, NRAMP family
1094	peptidase, U32 family
1116	HPr(Ser) kinase/phosphatase (hprK)
1130	oxidoreductase
1148	signal recognition particle-docking protein FtsY (ftsY)
1152	Cof family protein
1156	Cof family protein
1172	vicX protein (vicX)
1176	sensory box sensor histidine kinase (vicK)
1180	DNA-binding response regulator (vicR)
1184	amino acid ABC transporter, ATP-binding protein
1188	amino acid ABC transporter, amino acid-binding protein (fliY)
1192	amino acid ABC transporter, permease protein
1196	amino acid ABC transporter, permease protein
1208	DNA-binding response regulator (vicR)
1210	threonyl-tRNA synthetase (thrS)
1214	glycosyl transferase, group 1
1218	glycosyl transferase, group 1 (cpoA)
1222	alpha-amylase (amy)
1230	proline dipeptidase (pepQ)
1238	haloacid dehalogenase-like hydrolase superfamily
1244	mannonate dehydratase (uxuA)
1248	glucuronate isomerase
1254	transcriptional regulator, GntR family
1268	sodiumgalactoside symporter family protein
1270	D-isomer specific 2-hydroxyacid dehydrogenase family protein
1282	transcriptional regulator, LysR family
1290	ABC transporter, ATP-binding protein (potA)
1296	DedA family protein
1308	MutT/nudix family protein family
1310	phosphoserine phosphatase SerB (serB)

1312	septation ring formation regulator EzrA
1320	hydrolase, haloacid dehalogenase-like family (gph)
1340	sensor histidine kinase (vncS)
1348	transmembrane protein Vexp3 (vex3)
1352	ABC transporter, ATP-binding protein (vex2)
1358	transmembrane protein Vexp1 (vex1)
1366	transposase
1374	integrase, phage family
1390	holin 2
1398	minor structural protein
1400	host specificity protein
1404	minor structural protein
1406	PblA
1486	homeobox protein drg11
1488	reverse transcriptase
1496	p22 erf-like protein
1498	gp157
1500	tropomyosin 2
1512	gp49 homologous
1526	transcriptional regulator-related protein
1566	chorismate mutase
1572	PTS system component
1576	PTS system, IIB component
1580	PTS system IIA component
1584	lactose phosphotransferase system repressor (lacR)
1594	adhesion lipoprotein (lmb)
1602	GTP pyrophosphokinase (relA)
1606	2`,3`-cyclic-nucleotide 2`-phosphodiesterase (cpdB)
1616	iron ABC transporter, iron-binding protein
1620	DNA-binding response regulator
1630	PTS system component
1634	PTS system component (manM)
1638	PTS system component (manL)
1642	PTS system component
1658	response regulator BlpR (blpR)
1676	phosphate transport system regulatory protein PhoU
1680	phosphate ABC transporter, ATP-binding protein (pstB)
1684	phosphate ABC transporter, permease protein (pstA)
1690	phosphate ABC transporter, permease protein (pstC)
1694	probable hemolysin precursor
1704	ribosomal protein L11 methyltransferase (prmA)
1710	transcriptional regulator, MerR family (skgA)
1714	acetyltransferase, GNAT family
1716	MutT/nudix family protein
1722	spermidine N1-acetyltransferase
1726	ATPase, AAA family
1736	ABC transporter domain protein
1738	Helix-turn-helix domain protein
1748	integrase, phage family
1756	Helix-turn-helix domain protein
1762	bacteriophage L54a, integrase
1768	LPXTG-motif cell wall anchor domain protein
1776	membrane protein
1778	conjugal transfer protein
1780	IS1381, transposase OrfA/OrfB, truncation
1802	transcriptional regulator (rstR-1)
1806	transcriptional regulator
1808	FtsK/SpoIIIE family protein
1814	aggregation substance

1818	mercuric reductase
1822	transcriptional regulator, MerR family
1824	Mn2+/Fe2+ transporter, NRAMP family
1830	ABC transporter, ATP-binding protein (epiF)
1848	Helix-turn-helix domain protein
1850	type 2 phosphatidic acid phosphatase(PAP2), family
1858	Abortive infection protein family
1868	aminotransferase, class-V
1874	glutathione reductase (gor)
1882	chorismate synthase (aroC)
1886	3-dehydroquinate synthase (aroB)
1900	sulfatase family protein
1914	ABC transporter, ATP-binding protein
1920	smf protein (Smffamily)
1924	transferrin receptor
1928	iron compound ABC transporter, ATP-binding protein
1932	iron compound ABC transporter, permease protein
1942	acetyltransferase, CysE/LacA/LpxA/NodL family
1952	GTP-binding protein
1958	carbon starvation protein A
1960	response regulator (lytR)
1962	GAF domain protein (lytS)
2000	extracellular protein
2004	diarrheal toxin (yukA)
2024	carbamoyl-phosphate synthase, large subunit (carB)
2028	carbamoyl-phosphate synthase, small subunit (carA)
2032	aspartate carbamoyltransferase (pyrB)
2036	dihydroorotase, multifunctional complex type (pyrC)
2040	orotate phosphoribosyltransferase (pyrE)
2048	membrane protein
2062	phosphate ABC transporter, permease protein (pstA-2)
2064	phosphate ABC transporter, ATP-binding protein (pstB)
2070	phosphate transport system regulatory protein PhoU
2072	aminopeptidase N (pepN)
2076	DNA-binding response regulator (arlR)
2080	sensor histidine kinase (arlS)
2088	signal recognition particle protein (ffh)
2102	peptide ABC transporter, peptide-binding protein
2104	integrase/recombinase, phage integrase family
2108	sensor histidine kinase
2112	DNA-binding response regulator (vicR)
2118	ABC transporter, ATP-binding protein
2122	nisin-resistance protein
2130	lipoprotein
2136	gid protein (gid)
2140	transcriptional regulator, GntR family
2142	GMP synthase (guaA)
2152	branched-chain amino acid ABC transporter, permease protein (livM)
2154	branched-chain amino acid ABC transporter, ATP-binding protein (livG)
2156	branched-chain amino acid ABC transporter, ATP-binding protein (livF)
2160	acetoin utilization protein AcuB
2174	DNA polymerase III, delta prime subunit (holB)
2186	copper homeostasis protein (cutC)
2190	phosphoserine aminotransferase (serC)
2202	methylated-DNA–protein-cysteine S-methyltransferase (ogt)
2208	exodeoxyribonuclease III (xth)
2214	PTS system, IIC component
2224	tellurite resistance protein TehB (tehB)
2246	icaA protein

2250	acetyltransferase, GNAT family
2258	oxidoreductase, short chain dehydrogenase/reductase family (fabG)
2266	oxidoreductase, Gfo/Idh/MocA family family
2268	glyoxalase family protein
2272	UDP-N-acetylglucosamine pyrophosphorylase (glmU)
2276	MutT/nudix family protein
2284	5-methylthioadenosine/S-adenosylhomocysteine nucleosidase (mtf)
2296	phosphatidate cytidylyltransferase (cdsA)
2300	membrane-associated zinc metalloprotease
2308	autolysin (flgJ)
2312	DNA polymerase III, alpha subunit, Gram-positive type
2320	nitroreductase family protein superfamily
2326	4-hydroxy-2-oxoglutarate aldolase/2-deydro-3-deoxyphosphogluconate aldo
2328	carbohydrate kinase, PfkB family
2336	oxidoreductase, short chain dehydrogenase/reductase family (fabG)
2338	PTS system, IIA component (manL)
2342	glucuronyl hydrolase
2346	PTS system, IIB component (manL)
2350	PTS system, IIC component (manM)
2364	sugar binding transcriptional regulator RegR (regR)
2368	polypeptide deformylase (def)
2380	oxidoreductase, Gfo/Idh/MocA family
2382	endopeptidase O (pepO)
2394	Na+/H+ antiporter
2404	transcriptional regulator
2410	replication initiation protein RepRC
2412	bacteriophage L54a, antirepressor
2416	e11
2422	replicative DNA helicase (dnaB)
2432	GTP-binding protein
2440	arpR protein
2444	gene 17 protein
2458	integrase/recombinase, phage integrase family
2468	bacteriophage L54a, phage D3 terminase
2472	protease
2500	PblB
2504	sensor histidine kinase
2514	N-acetylmuramoyl-L-alanine amidase
2518	KH domain protein
2522	ribosomal protein S16 (rpsP)
2526	permease
2528	ABC transporter, ATP-binding protein
2538	carbamoyl-phosphate synthase, large subunit
2540	carbamoyl-phosphate synthase, small subunit (carA)
2550	transcriptional regulator, LysR family
2554	ribosomal protein L27 (rpmA)
2562	ribosomal protein L21 (rplU)
2572	glycerophosphoryl diester phosphodiesterase
2582	nitroreductase family protein
2586	dipeptidase (pepV)
2614	GTP-binding protein HflX (hflX)
2618	galactose-1-phosphate uridylyltransferase (galT)
2626	oxidoreductase, short chain dehydrogenase/reductase family
2630	single-stranded-DNA-specific exonuclease RecJ (recJ)
2638	adenine phosphoribosyltransferase (apt)
2646	Bcl-2 family protein
2654	oxidoreductase, DadA family protein
2658	glucose-1-phosphate thymidylyltransferase (rfbA)
2664	dTDP-4-dehydrorhamnose 3,5-epimerase (rfbC)

2682	hyaluronidase
2686	mutator MutT protein (mutX)
2690	MutT/nudix family protein
2694	membrane protein
2702	acetolactate synthase (ilvK)
2706	adherence and virulence protein A (pavA)
2714	ABC transporter, permease protein (rbsC)
2722	metallo-beta-lactamase superfamily protein
2734	ribose 5-phosphate isomerase (rpiA)
2738	phosphopentomutase (deoB)
2742	purine nucleoside phosphorylase, family 2 (deoD)
2750	purine nucleoside phosphorylase (deoD)
2762	capsular polysaccharide biosynthesis protein Cps4A (cps4A)
2768	cpsb protein
2770	cpsc protein
2772	CpsE
2774	CpsF
2776	CpsVG
2778	CpsVH
2780	CpsVM
2782	CpsVN
2784	glycosyl transferase domain protein
2786	glycosyl transferase, family 2/glycosyl transferase family 8
2790	CpsVK
2794	CpsL
2796	neuB protein
2798	UDP-N-acetylglucosamine 2-epimerase
2800	hexapeptide transferase family protein
2802	NeuA
2808	uracil-DNA glycosylase (ung)
2818	DNA topoisomerase IV, B subunit (parE)
2822	DNA topoisomerase IV, A subunit (parC)
2826	branched-chain amino acid aminotransferase (ilvE)
2842	glycerol kinase (glpK)
2848	aerobic glycerol-3-phosphate dehydrogenase (glpD)
2874	ABC transporter, ATP-binding protein
2882	PTS system component (bglP)
2886	glutamate 5-kinase (proB)
2890	gamma-glutamyl phosphate reductase (proA)
2898	cell division protein FtsL (ftsL)
2904	penicillin-binding protein 2X (pbpX)
2910	phospho-N-acetylmuramoyl-pentapeptide-transferase (mraY)
2914	ATP-dependent RNA helicase, DEAD/DEAH box family (deaD)
2918	ABC transporter, substrate-binding protein
2924	amino acid ABC transporter, permease protein
2928	amino acid ABC transporter, ATP-binding protein
2932	thioredoxin reductase (trxB)
2940	NAD+ synthetase (nadE)
2944	aminopeptidase C (pepC)
2952	recombination protein U (recU)
2966	Uncharacterized protein family UPF0020 family
2974	autoinducer-2 production protein LuxS (luxS)
2978	KH domain protein
2986	ABC transporter, ATP-binding protein
2994	DNA-binding response regulator (vraR)
3000	guanylate kinase (gmk)
3004	DNA-directed RNA polymerase, omega subunit
3008	primosomal protein N (priA)
3012	methionyl-tRNA formyltransferase (fmt)

3016	Sun protein (sun)
3020	protein phosphatase 2C
3032	sensor histidine kinase
3034	DNA-binding response regulator (vraR)
3036	cof family protein/peptidyl-prolyl cis-trans isomerase, cyclophilin typ
3040	S1 RNA binding domain protein (rpsA)
3044	pyruvate formate-lyase-activating enzyme
3062	PTS system, IIB component (celA)
3066	PTS system, cellobiose-specific IIC component (celB)
3068	formate acetyltransferase (pfl)
3072	transaldolase
3080	cysteine synthase A (cysK)
3088	comF operon protein 1 (comFA)
3092	competence protein ComF
3096	ribosomal subunit interface protein (yfiA)
3104	tryptophanyl-tRNA synthetase (trpS)
3108	carbamate kinase (arcC)
3116	ornithine carbamoyltransferase (argF)
3124	arginine deiminase (arcA)
3134	transcriptional regulator, Crp/Fnr family
3138	inosine-5'-monophosphate dehydrogenase (guaB)
3140	MutR
3142	transporter
3146	recF protein (recF)
3158	peptidase, M16 family
3166	ABC transporter, ATP-binding protein
3170	ABC transporter, ATP-binding protein
3178	LysM domain protein (lytN)
3180	immunodominant antigen A (isaA)
3184	L-serine dehydratase, iron-sulfur-dependent, alpha subunit (sdhA)
3188	L-serine dehydratase, iron-sulfur-dependent, beta subunit (sdhB)
3202	DHH subfamily 1 protein
3206	ribosomal protein L9 (rplI)
3210	replicative DNA helicase (dnaB)
3216	ribosomal protein S4 (rpsD)
3224	transcriptional regulator, TetR family
3236	membrane protein
3238	choline transporter (proWX)
3240	glycine betaine/L-proline transport ATP binding subunit (proV)
3242	DNA-binding response regulator
3244	Histidine kinase-, DNA gyrase B-, phytochrome-like ATPase family
3246	ornithine carbamoyltransferase (argF)
3248	carbamate kinase (arcC)
3252	membrane protein
3256	sensory box histidine kinase VicK
3258	DNA-binding response regulator
3268	Helix-turn-helix domain protein
3278	integrase
3284	ribosomal protein L33 (rpmG)
3288	ribosomal protein L32 (rpmF)
3300	YitT family protein
3304	YitT family protein
3320	DNA mismatch repair protein MutS (mutS)
3324	cold-shock domain family protein-related protein
3336	drug transporter
3340	Holliday junction DNA helicase RuvA (ruvA)
3352	recA protein (recA)
3386	oxidoreductase, Gfo/Idh/MocA family
3390	acetyltransferase, GNAT family

3394	anaerobic ribonucleoside-triphosphate reductase activating protein (nrd
3412	ABC transporter, permease protein (rbsC)
3414	ABC transporter, ATP-binding protein (nrtC)
3416	PTS system, mannose-specific IIAB components (manL)
3420	Cof family protein
3432	xanthine/uracil permease family protein
3440	acetyltransferase, GNAT family
3442	transcriptional regulator (cps4A)
3448	HIT family protein (hit)
3460	ABC transporter, permease protein
3472	Uncharacterized BCR, YhbC family COG0779 superfamily
3484	ribosomal protein L7A family
3496	esterase
3500	transcriptional repressor, CopY (copY)
3504	cation-transporting ATPase, E1-E2 family
3508	cation-binding protein-related protein
3520	DNA polymerase I (polA)
3534	DNA-binding response regulator (saeR)
3536	sensor histidine kinase (saeS)
3562	drug resistance transporter, EmrB/QacA subfamily
3566	peptidase M24 family protein
3570	peptidase M24 family protein (pepQ)
3572	cytidine/deoxycytidylate deaminase family protein
3584	translation elongation factor P (efp)
3592	N utilization substance protein B (nusB)
3596	sugar-binding transcriptional regulator, LacI family (scrR)
3600	sucrose-6-phosphate dehydrogenase (scrB)
3606	PTS system IIABC components (scrA)
3610	fructokinase (scrK)
3614	mannose-6-phosphate isomerase, class I (manA)
3622	phospho-2-dehydro-3-deoxyheptonate aldolase (aroH)
3626	holo-(acyl-carrier-protein) synthase (acpS)
3630	alanine racemase (alr)
3634	autolysin (usp45)
3636	ATP-dependent DNA helicase RecG (recG)
3642	shikimate 5-dehydrogenase (aroE)
3652	Cof family protein
3668	ferredoxin-related protein
3676	peptidase t (pepT)
3684	UDP-N-acetylmuramoylalanyl-D-glutamate--2,6-diaminopimelate ligase (mur
3692	iron compound ABC transporter, substrate-binding protein
3698	FecCD transport family protein (sirB)
3704	iron compound ABC transporter, permease protein (sirB)
3710	inorganic pyrophosphatase, manganese-dependent (ppaC)
3714	pyruvate formate-lyase-activating enzyme (pflA)
3718	CBS domain protein
3730	acid phosphatase
3736	LPXTG-motif cell wall anchor domain protein
3738	LPXTG-site transpeptidase family protein
3742	LPXTG-site transpeptidase family protein
3744	cell wall surface anchor family protein
3746	cell wall surface anchor family protein
3752	glycosyl transferase, group 1 family protein domain protein
3754	EpsQ protein
3756	polysaccharide extrusion protein
3768	dTDP-glucose 4-6-dehydratase
3782	glycosyl transferase domain protein
3788	dTDP-4-dehydrorhamnose reductase (rfbD)
3796	RNA polymerase sigma-70 factor (rpoD)

3802	DNA primase (dnaG)
3816	ABC transporter, ATP-binding protein Vexp2 (vex2)
3818	permease
3820	transmembrane protein Vexp3
3822	transmembrane protein Vexp3
3832	endopeptidase O (pepO)
3834	endopeptidase O (pepO)
3840	serine protease, subtilase family
3842	exotoxin 2
3844	CylK
3854	glycine cleavage system T protein
3856	CylE
3858	ABC transporter homolog CylB
3862	acyl carrier protein homolog AcpC (acpP)
3864	3-oxoacyl-(acyl-carrier-protein) reductase (fabG)
3868	CylD
3876	membrane protein
3912	LPXTG-site transpeptidase family protein
3916	LPXTG-site transpeptidase family protein
3918	LPXTG-site transpeptidase family protein
3920	LPXTG-motif cell wall anchor domain protein
3928	chaperonin, 33 kDa (hslO)
3932	Tn5252, Orf 10 protein
3934	transposase OrfAB, subunit B
3948	psr protein
3952	shikimate kinase (aroK)
3964	enolase (eno)
3972	MutT/nudix family protein
3976	glycosyl transferase, group 1
3978	preprotein translocase, SecA subunit (secA)
3986	preprotein translocase SecY family protein
3990	glycosyl transferase, family 8
3992	glycosyl transferase, family 2
3998	glycosyl transferase, family 8
4000	glycosyl transferase, family 2/glycosyl transferase family 8
4002	glycosyl transferase, family 8
4012	LPXTG-motif cell wall anchor domain protein (clfB)
4016	transcriptional regulator
4018	excinuclease ABC, B subunit (uvrB)
4022	Abortive infection protein family
4024	amino acid ABC transporter, amino acid-binding protein/permease protein
4026	amino acid ABC transporter, ATP-binding protein
4034	GTP-binding protein, GTP1/Obg family (obg)
4042	aminopeptidase PepS (pepS)
4050	ribosomal small subunit pseudouridine synthase A (rsuA)
4060	lactoylglutathione lyase (gloA)
4064	glycosyl transferase family protein
4072	alkylphosphonate utilization operon protein PhnA (phnA)
4078	glucosamine--fructose-6-phosphate aminotransferase (isomerizing) (glmS)
4090	Phosphofructokinase
4094	DNA polymerase III, alpha subunit (dnaE)
4098	transcriptional regulator, GntR family
4102	ABC transporter, ATP-binding protein
4106	ABC transporter, ATP-binding protein
4116	FtsK/SpoIIIE family protein
4122	Helix-turn-helix domain protein
4152	Helix-turn-helix domain protein
4158	excisionase
4160	transposase

4166	chloramphenicol acetyltransferase (cat)
4174	PilB-related protein
4178	acetyltransferase
4182	Leucine Rich Repeat domain protein
4190	nucleoside diphosphate kinase (ndk)
4206	Protein of unknown function superfamily
4218	hydrolase, haloacid dehalogenase-like family (pho2)
4226	oxygen-independent coproporphyrinogen III oxidase
4236	phosphoglucomutase/phosphomannomutase family protein (femD)
4240	Gram-positive signal peptide, YSIRK family domain protein
4256	cobyric acid synthase (cobQ)
4260	lipoate-protein ligase A (lplA)
4264	branched-chain alpha-keto acid dehydrogenase E3 component, lipoamide de
4266	pyruvate dehydrogenase complex, E2 component, dihydrolipoamide acetyltr
4270	pyruvate dehydrogenase complex, E1 component, pyruvate dehydrogenase be
4286	magnesium transporter, CorA family
4294	exonuclease RexB (rexB)
4302	phenylalanyl-tRNA synthetase, beta subunit (pheT)
4324	ATP synthase F1, epsilon subunit (atpC)
4328	ATP synthase F1, beta subunit (atpD)
4332	ATP synthase F1, gamma subunit (atpG)
4338	ATP synthase F1, alpha subunit (atpA)
4342	ATP synthase F1, delta subunit (atpH)
4346	ATP synthase F0, B subunit (atpF)
4350	ATP synthase, F0 subunit A (atpB)
4354	proton-translocating ATPase, c subunit-related protein
4360	glycogen synthase (glgA)
4362	glycogen biosynthesis protein GlgD (glgD)
4366	1,4-alpha-glucan branching enzyme (glgB)
4368	pullulanase
4382	ribonuclease BN
4396	acetyltransferase, GNAT family
4398	UDP-N-acetylglucosamine 1-carboxyvinyltransferase (murA)
4402	thiamine-phosphate pyrophosphorylase (thiE)
4406	phosphomethylpyrimidine kinase (thiD)
4410	transcriptional regulator, Deg family (tenA)
4414	ABC transporter, ATP-binding protein
4426	S-adenosylmethionine synthetase (metK)
4440	DNA polymerase III, gamma and tau subunits (dnaX)
4444	GAF domain protein
4448	uridine kinase (udk)
4452	ATP-dependent RNA helicase, DEAD/DEAH box family
4458	peptidoglycan GlcNAc deacetylase (pgdA)
4462	glyceraldehyde-3-phosphate dehydrogenase, NADP-dependent (gapN)
4466	phosphoenolpyruvate-protein phosphotransferase (ptsI)
4470	phosphocarrier protein hpr
4474	NrdH-redoxin-related protein
4478	ribonucleoside-diphosphate reductase 2, alpha subunit (nrdE)
4498	glycosyl transferase, family 8
4504	alanyl-tRNA synthetase (alaS)
4512	alkyl hydroperoxide reductase, subunit F (ahpF)
4516	alkyl hydroperoxide reductase, subunit C (ahpC)
4520	ribosomal protein S2 (rpsB)
4524	translation elongation factor Ts (tsf)
4532	transcriptional regulator CtsR (ctsR)
4536	ATP-dependent Clp protease, ATP-binding subunit (clpC)
4540	deoxynucleoside kinase
4544	NifR3/Smm1 family protein
4548	chaperonin, 33 kDa (hslO)

4558	glutamate--cysteine ligase (gshA)
4562	Helix-turn-helix domain, fis-type protein
4566	perfringolysin O regulator protein (pfoR)
4570	adenylosuccinate synthetase (purA)
4578	SgaT protein (sgaT)
4582	PTS system, IIB component (sgaT)
4586	PTS system, IIA component (mtlA)
4590	hexulose-6-phosphate synthase
4594	hexulose-6-phosphate isomerase
4598	L-ribulose-5-phosphate 4-epimerase (araD)
4606	sugar binding transcriptional regulator RegR
4610	D-isomer specific 2-hydroxyacid dehydrogenase family protein (serA)
4622	transcriptional regulator, BglG family
4632	glycine betaine/L-proline transport ATP binding subunit (proV)
4636	amino acid ABC transporter, permease protein
4644	Na+/H+ exchanger family protein (kefB)
4648	glyoxylase family protein
4652	LPXTG-site transpeptidase family protein
4656	DNA gyrase, A subunit (gyrA)
4660	L-lactate dehydrogenase (ldh)
4664	NADH oxidase (nox)
4680	lipoprotein (bmpD)
4690	pantothenate kinase (coaA)
4694	ribosomal protein S20 (rpsT)
4698	amino acid ABC transporter, amino acid-binding protein (aatB)
4702	amino acid ABC transporter, ATP-binding protein
4726	ribosomal large subunit pseudouridine synthase B (rluB)
4734	Uncharacterized ACR, COG1354
4738	integrase/recombinase, phage integrase family (xerD)
4742	CBS domain protein
4746	phosphoesterase
4750	HAM1 protein
4768	transcriptional regulator, biotin repressor family
4792	amino acid ABC transproter, permease protein
4796	amino acid ABC transporter, substrate-binding protein
4798	6-aminohexanoate-cyclic-dimer hydrolase
4800	transcription elongation factor GreA (greA)
4804	Uncharacterized BCR, YceG family COG1559
4812	UDP-N-acetylmuramate--alanine ligase (murC)
4822	Snf2 family protein
4828	GTP-binding protein (b2511)
4832	primosomal protein DnaI (dnaI)
4844	sensor histidine kinase (arlS)
4846	DNA-binding response regulator (arlR)
4852	heat shock protein HtpX (htpX)
4870	potassium uptake protein, Trk family
4874	ABC transporter, ATP-binding protein
4888	phosphoglycerate kinase (pgk)
4896	transcriptional regulator, MerR family
4900	glutamine synthetase, type I (glnA)
4904	secreted 45 kd protein (usp45)
4908	metallo-beta-lactamase superfamily protein
4916	glycoprotease family protein
4926	glycoprotease family protein (gcp)
4938	ribosomal protein S14p/S29e (rpsN)
4952	exonuclease (dnaQ)
4956	transcriptional regulator, merR family
4958	cyclopropane-fatty-acyl-phospholipid synthase (cfa)
4970	1,4-dihydroxy-2-naphthoate octaprenyltransferase (menA)

4972	pyridine nucleotide-disulphide oxidoreductase (ndh)
4974	cytochrome d oxidase, subunit I (cydA)
4976	cytochrome d ubiquinol oxidase, subunit II (cydB)
4980	transport ATP-binding protein CydD
4988	polyprenyl synthetase (ispB)
4990	X-pro dipeptidyl-peptidase (pepX)
4998	drug transporter
5002	universal stress protein family
5004	glycerol uptake facilitator protein (glpF)
5012	cppA protein (cppA)
5034	exodeoxyribonuclease V, alpha subunit (recD)
5038	Signal peptidase I
5042	ribonuclease HIII (rnhC)
5062	transcriptional regulator
5068	maltose ABC transporter, permease protein (malD)
5072	maltose ABC transporter, permease protein (malC)
5088	ABC transporter, ATP-binding protein
5092	ABC transporter, permease protein
5106	spspoJ protein (spo0J)
5114	DNA polymerase III, beta subunit (dnaN)
5118	Diacylglycerol kinase catalytic domain (presumed) protein
5138	transcription-repair coupling factor (mfd)
5142	S4 domain protein
5156	MesJ/Ycf62 family protein
5160	hypoxanthine phosphoribosyltransferase (hpt)
5164	cell division protein FtsH (ftsH)
5172	hydrolase, haloacid dehalogenase-like family (b2690)
5178	transcriptional regulator, MarR family
5182	3-oxoacyl-(acyl-carrier-protein) synthase III (fabH)
5190	enoyl-(acyl-carrier-protein) reductase (fabK)
5194	malonyl CoA-acyl carrier protein transacylase (fabD)
5198	3-oxoacyl-[acyl-carrier protein] reductase (fabG)
5200	3-oxoacyl-(acyl-carrier-protein) synthase II (fabF)
5202	acetyl-CoA carboxylase, biotin carboxyl carrier protein (accB)
5206	(3R)-hydroxymyristoyl-(acyl-carrier-protein) dehydratase (fabZ)
5210	acetyl-CoA carboxylase, biotin carboxylase (accC)
5214	acetyl-CoA carboxylase, carboxyl transferase, beta subunit (accD)
5218	acetyl-CoA carboxylase, carboxyl transferase, alpha subunit (accA)
5224	seryl-tRNA synthetase (serS)
5234	PTS system, mannose-specific IID component
5246	ribosomal large subunit pseudouridine synthase, RluD subfamily (rluD)
5254	GTP pyrophosphokinase (relA)
5266	ribose-phosphate pyrophosphokinase (prsA)
5270	aminotransferase, class-V
5274	DNA-binding protein
5282	Domain of unknown function
5290	platelet activating factor
5296	transcriptional regulator, AraC family
5302	voltage-gated chloride channel family protein
5318	spermidine/putrescine ABC transporter, ATP-binding protein (potA)
5320	UDP-N-acetylenolpyruvoylglucosamine reductase (murB)
5324	bifunctional folate synthesis protein (folK)
5328	dihydroneopterin aldolase (folB)
5332	dihydropteroate synthase (folP)
5336	GTP cyclohydrolase I (folE)
5344	rarD protein (rarD)
5348	homoserine kinase (thrB)
5354	Polysaccharide deacetylase family (icaB)
5362	osmoprotectant transporter, BCCT family (opuD)

5384	thiol peroxidase (psaD)
5388	hydrolase
5390	transcriptional regulator, GntR family
5402	gls24 protein
5424	uncharacterized domain 1
5440	cation efflux family protein
5454	dihydroorotate dehydrogenase A (pyrDa)
5458	beta-lactam resistance factor (fibB)
5462	beta-lactam resistance factor (fibA)
5474	HD domain protein
5482	cation-transporting ATPase, E1-E2 family
5486	fructose-1,6-bisphosphatase (fbp)
5488	iron-sulfur cluster-binding protein
5492	peptide chain release factor 2 (prfB)
5496	cell division ABC transporter, ATP-binding protein FtsE (ftsE)
5504	carboxymethylenebutenolidase-related protein
5506	metallo-beta-lactamase superfamily protein
5514	DNA polymerase III, epsilon subunit/ATP-dependent helicase DinG
5520	asparaginyl-tRNA synthetase (asnS)
5526	inosine-uridine preferring nucleoside hydrolase (iunH)
5528	general stress protein 170
5534	Uncharacterised protein family superfamily
5538	Uncharacterized BCR, COG1481
5546	zinc ABC transporter, zinc-binding adhesion liprotein (adcA)
5560	isochorismatase family protein (entB)
5566	3-hydroxybutyryl-CoA dehydrogenase
5572	pyruvate phosphate dikinase (ppdK)
5574	glutamyl-tRNA(Gln) amidotransferase, C subunit (gatC)
5580	glutamyl-tRNA(Gln) amidotransferase, A subunit (gatA)
5594	GTP-binding protein
5612	iojap-related protein
5626	transcriptional regulator SkgA (skgA)
5630	glycerol uptake facilitator protein (glpF)
5634	dihydroxyacetone kinase family protein
5638	dihydroxyacetone kinase family protein
5640	transcriptional regulator, tetR family
5646	dihydroxyacetone kinase family protein
5654	glutamine amidotransferase, class I
5666	peptidase, M20/M25/M40 family
5668	ABC transporter, ATP-binding protein
5686	pur operon repressor (purR)
5690	cmp-binding-factor 1 (cbf1)
5694	competence-induced protein Ccs50 (ccs50)
5702	ribulose-phosphate 3-epimerase (rpe)
5710	rRNA (guanine-N1-)-methyltransferase (rrmA)
5712	dimethyladenosine transferase (ksgA)
5718	primase-related protein
5726	endosome-associated protein
5728	CG17785 gene product
5734	dltD protein (dltD)
5738	D-alanyl carrier protein-related protein
5742	dltB protein (dltB)
5754	DNA-binding response regulator (arlR)
5756	ribosomal protein L34 (rpmH)
5766	penicillin-binding protein 4 (pbp4)
5770	intein-containing protein
5774	NifU family protein
5778	aminotransferase, class-V
5782	Uncharacterized protein family (UPF0051) family

5786	ABC transporter, ATP-binding protein
5790	glycosyl transferase domain protein (llm)
5794	transcriptional regulator MecA (mecA)
5798	undecaprenol kinase
5806	amino acid ABC transporter, amino acid-binding protein/permease protein
5808	amino acid ABC transporter, ATP-binding protein
5834	riboflavin biosynthesis protein RibF (ribF)
5850	type I restriction-modification system, S subunit
5860	lipoprotein
5862	aggregation substance
5866	ID479
5896	type II DNA modification methyltransferase Spn5252IP (spn5252IMP)
5916	ribosomal protein L10 (rplJ)
5922	ATP-dependent Clp protease, ATP-binding subunit ClpC (clpC)
5926	homocysteine S-methyltransferase (mmuM)
5932	transcriptional regulator, TetR family
5938	GTP-binding protein (cgpA)
5952	thymidylate synthase (thyA)
5956	condensing enzyme, FabH-related
5960	hydroxymethylglutaryl-CoA reductase, degradative
5974	gene_idK21C13.21~pir||T04769~strong similarity to unknown protein, put
5976	FMN-dependent dehydrogenase family protein
5980	phosphomevalonate kinase
5986	diphosphomevalonate decarboxylase (mvaD)
5990	mevalonate kinase (mvk)
5994	Histidine kinase-, DNA gyrase B-, phytochrome-like ATPase family (PhoR1
6002	GTP pyrophosphokinase (relA)
6006	transposase for insertion sequence element is904
6016	5'-nucleotidase family
6018	polypeptide deformylase (def)
6022	NADP-specific glutamate dehydrogenase (gdhA)
6026	ABC transporter, ATP-binding/permease protein
6028	ABC transporter, ATP-binding/permease protein
6030	acetyltransferase, GNAT family family
6032	ABC transporter, ATP-binding protein
6040	degV family protein (degV)
6056	carbohydrate kinase, PfkB family (fruB)
6064	beta-lactam resistance factor (fibB)
6070	2-dehydropantoate 2-reductase
6076	PTS system component
6078	pyridine nucleotide-disulphide oxidoreductase family protein (trxB)
6082	tRNA (guanine-N1)-methyltransferase (trmD)
6092	c5a peptidase precursor
6100	ParA
6102	transposase family protein (orfA)
6116	Tn5252, relaxase
6120	Tn5252, Orf 10 protein
6124	mercuric reductase
6126	transcriptional regulator, MerR family
6132	cation transport ATPase, E1-E2 family
6138	cation-transporting ATPase, E1-E2 family
6140	cation-transporting ATPase, E1-E2 family
6144	cation-transporting ATPase, E1-E2 family
6146	transcriptional repressor, CopY (copY)
6150	cadmium resistance transporter
6158	membrane protein
6162	flavoprotein (dfp)
6170	lipoate-protein ligase A
6174	FMN oxidoreductase (nemA)

6178	Bacterial luciferase superfamily
6182	glycine cleavage system H protein (gcvH)
6186	Domain of unknown function
6194	lipoate-protein ligase A (lplA)
6198	formate--tetrahydrofolate ligase (fhs)
6202	cardiolipin synthetase (cls)
6220	aminotransferase, class II (aspB)
6222	RNA methyltransferase, TrmH family, group 2
6232	60 kda chaperonin
6242	purine nucleoside phosphorylase (deoD)
6248	deoxyribose-phosphate aldolase (deoC)
6254	Lyme disease proteins of unknown function
6258	ribosomal large subunit pseudouridine synthase, RluD subfamily (rluD)
6262	penicillin-binding protein 2A (pbp2A)
6266	pathenogenicity protein
6268	transcription antitermination protein NusG (nusG)
6272	glycosyl transferase, family 8
6276	glycosyl transferase, family 8
6284	sugar transporter family protein
6292	sensory box histidine kinase
6306	homocysteine S-methyltransferase (metH)
6310	glycerol dehydrogenase
6312	DNA topology modulation protein FlaR
6316	translation initiation factor IF-1 (infA)
6320	adenylate kinase (adk)
6326	ribosomal protein L15 (rplO)
6330	ribosomal protein L30 (rpmD)
6336	ribosomal protein S5 (rpsE)
6344	ribosomal protein L6 (rplF)
6348	ribosomal protein S8 (rpsH)
6352	ribosomal protein S14 (rpsN)
6356	ribosomal protein L5 (rplE)
6360	ribosomal protein L24 (rplX)
6366	ribosomal protein L14 (rplN)
6368	ribosomal protein S17 (rpsQ)
6372	ribosomal protein L29 (rpmC)
6374	ribosomal protein L16 (rplP)
6378	ribosomal protein S3 (rpsC)
6382	ribosomal protein L22 (rplV)
6386	ribosomal protein S19 (rpsS)
6390	ribosomal protein L2 (rplB)
6394	ribosomal protein L23 (rplW)
6398	ribosomal protein L4/L1 family (rplD)
6402	ribosomal protein L3 (rplC)
6408	ribosomal protein S10 (rpsJ)
6414	MATE efflux family protein
6418	threonine synthase (thrC)
6428	Uncharacterized BCR, COG1636 superfamily
6436	4-alpha-glucanotransferase (malQ)
6440	glycogen phosphorylase family protein (malP)
6444	glycerol-3-phosphate transporter (glpT)
6452	rhodanese family protein
6458	ammonium transporter
6464	DNA repair protein RadA (radA)
6472	oxidoreductase, pyridine nucleotide-disulfide, class I
6478	ribose ABC transporter, periplasmic D-ribose-binding protein (rbsB)
6484	ribose ABC transporter, ATP-binding protein (rbsA)
6486	ribose ABC transporter protein (rbsD)
6488	ribokinase (rbsK)

6498	ABC transporter, ATP-binding protein
6502	DNA-binding response regulator (vicR)
6506	argininosuccinate synthase (argG)
6508	argininosuccinate lyase (argH)
6514	bacteriophage L54a, repressor protein
6528	soluble transducer HtrXIII
6542	probable transposase (insertion sequence IS861)
6544	ABC transporter, ATP-binding/permease protein
6550	ABC transporter, ATP-binding/permease protein
6560	Serine hydroxymethyltransferase
6568	HemK protein (hemK)
6572	peptide chain release factor 1 (prfA)
6576	thymidine kinases
6580	4-oxalocrotonate tautomerase (dmpI)
6588	oxidoreductase
6594	oxidoreductase
6600	formate/nitrite transporter family protein
6608	xanthine permease (pbuX)
6612	xanthine phosphoribosyltransferase (xpt)
6616	guanosine monophosphate reductase (guaC)
6620	drug resistance transporter, EmrB/QacA subfamily
6622	oxidoreductase
6624	Kup system potassium uptake protein (kup)
6636	O-methyltransferase
6642	oligoendopeptidase F (pepF)
6646	competence protein ComA (comA)
6650	major facilitator superfamily protein superfamily
6652	ribosomal small subunit pseudouridine synthase A (rsuA)
6658	glucosamine-6-phosphate isomerase (nagB)
6662	nodulin-related protein, truncation
6664	S-adenosylmethioninetRNA ribosyltransferase-isomerase (queA)
6674	permease, GntP family
6684	6-phospho-beta-glucosidase (bglA)
6686	PTS system, beta-glucosides-specific IIABC components
6688	transcription antiterminator LicT (licT)
6704	esterase
6706	sugar-binding transcriptional repressor, LacI family
6708	hydrolase, haloacid dehalogenase-like family
6712	DNA internalization-related competence protein ComEC/Rec2
6716	competence protein CelA (celA)
6720	acyltransferase family protein
6732	ATP-dependent RNA helicase DeaD (deaD)
6736	lipoprotein, YaeC family
6738	ABC transporter, permease protein
6752	diacylglycerol kinase (dgkA)
6768	formamidopyrimidine-DNA glycosylase (mutM)
6776	epidermin immunity protein F
6788	glycyl-tRNA synthetase, beta subunit (glyS)
6790	acyl carrier protein phosphodiesterase
6800	SsrA-binding protein (smpB)
6822	D-alanine--D-alanine ligase
6824	recombination protein RecR (recR)
6830	penicillin-binding protein 2b
6832	phosphoglycerate mutase (gpmA)
6836	triosephosphate isomerase (tpiA)
6856	phosphoglycerate mutase family protein
6860	D-alanyl-D-alanine carboxypeptidase family
6864	autolysin
6868	heat-inducible transcription repressor HrcA (hrcA)

6872	heat shock protein GrpE (grpE)
6876	chaperone protein dnak
6880	dnaJ protein (dnaJ)
6884	transcriptional regulator, gntR family domain protein
6888	tRNA pseudouridine synthase A (truA)
6892	phosphomethylpyrimidine kinase (thiD)
6910	galactose-6-phosphate isomerase, LacA subunit (lacA)
6922	tagatose 1,6-diphosphate aldolase (lacD)
6932	sugar ABC transporter, ATP-binding protein (msmK)
6936	glucan 1,6-alpha-glucosidase (dexB)
6940	UDP-glucose 4-epimerase (galE)
6942	response regulator (citB)
6950	citrate carrier protein (citS)
6954	malate oxidoreductase (tme)
6958	bacterocin transport accessory protein
6976	transposase family protein (orfA)
6980	pXO1-128
6986	adhesion lipoprotein (lmb)
6994	DNA-directed RNA polymerase, alpha subunit (rpoA)
6998	ribosomal protein L17 (rplQ)
7040	probable dna-directed rna polymerase delta subunit
7044	CTP synthase (pyrG)
7058	bacteriocin transport accessory protein
7074	translation initiation factor IF-3 (infC)
7100	adenosine deaminase
8468	preprotein translocase, SecE subunit
8476	antigen, 67 kDa
8486	Lipase/Acylhydrolase
8492	peptide ABC transporter, permease protein (oppB)
8494	competence protein CglB (cglB)
8502	peptide ABC transporter, peptide-binding protein
8504	oxidoreductase
8510	amino acid ABC transporter, permease protein (opuBB)
8522	abc transporter atp-binding protein ybhf
8530	glycerol-3-phosphate dehydrogenase (NAD(P)+) (gpsA)
8538	sugar ABC transporter, sugar-binding protein
8544	secreted 45 kd protein (usp45)
8556	phosphoglycerate mutase family protein
8566	glycosyl hydrolase, family 3
8576	N-acetylmuramoyl-L-alanine amidase
8596	sensory box histidine kinase (withHAMPandPASd)
8608	aminoglycoside 6-adenylyltransferase
8622	iron compound ABC transporter, permease protein (sirB)
8636	phosphate ABC transporter, permease protein (pstC-2)
8650	branched-chain amino acid transport system II carrier protein (brnQ)
8658	PTS system, IID component
8662	replisome organiser-related protein
8674	alkaline amylopullulanase
8676	exfoliative toxin A
8690	glycerol uptake facilitator protein (glpF)
8698	ABC transporter, ATP-binding protein
8706	CDP-diacylglycerol--glycerol-3-phosphate 3-phosphatidyltransferase (pgs
8708	cobalt transport protein
8730	integral membrane protein
8734	yadS protein
8736	cell wall surface anchor family protein
8748	polysaccharide biosynthesis protein
8752	glycosyl transferase domain protein
8764	endopeptidase O

8770	beta-ketoacyl-acyl carrier protein synthase II
8772	ABC transporter, ATP-binding protein
8776	penicillin-binding protein
8778	cell wall surface anchor family protein
8780	cell wall surface anchor family protein
8786	LPXTG-motif cell wall anchor domain protein
8788	6-aminohexanoate-cyclic-dimer hydrolase
8796	NLP/P60 family protein
8802	DNA/RNA non-specific endonuclease
8806	hydroxyethylthiazole kinase (thiM)
8826	PTS system component
8832	sugar ABC transporter, permease protein
8836	potassium uptake protein, Trk family (trkA)
8850	lemA protein (lemA)
8856	cobalt transport protein
8882	spermidine/putrescine ABC transporter, spermidine/putrescine-binding pr
8884	spermidine/putrescine ABC transporter, permease protein (potC)
8906	ABC transporter, substrate-binding protein
8908	lipoprotein
8916	sensor histidine kinase
8930	TrsK-like protein (traK)
8936	R5 protein
8962	chromosome assembly protein homolog
8978	ribose ABC transporter, permease protein (rbsC)
8980	permease
8982	sensor histidine kinase (arlS)
8986	hydrolase, haloacid dehalogenase-like family (gph)
8994	dephospho-CoA kinase
8996	oxalateformate antiporter
9004	sensory box protein
9006	host cell surface-exposed lipoprotein
9012	PAP2 family protein
9034	GtrA family protein
9050	lipoprotein signal peptidase (lspA)
9280	alcohol dehydrogenase, zinc-containing (adh)
9284	trigger factor (tig)
9290	fructose-bisphosphate aldolase (fba)
9292	DAK2 domain protein
9296	oligopeptide ABC transporter, permease protein
9298	N-acetylglucosamine-6-phosphate deacetylase (nagA)
9300	transcriptional regulator, DeoR family (lacR)
9302	PTS system, mannose-specific IIC component (manM)
9306	Phosphoglucose isomerase
9310	aspartate--ammonia ligase (asnA)
9312	amino acid ABC transporter, ATP-binding protein
9314	DNA-binding protein HU (hup)
9316	DHH subfamily 1 protein
9318	chloride channel
9320	integrase (int)
9324	DNA/RNA non-specific endonuclease
9326	PTS system component
9328	cell division protein, FtsW/RodA/SpoVE family (ftsW)
9330	LPXTG-motif cell wall anchor domain protein
9332	peptide chain release factor 3 (prfC)
9334	ABC transporter, ATP-binding protein
9336	superoxide dismutase [mn-fe]
9340	phenylalanyl-tRNA synthetase, alpha subunit (pheS)
9342	amino acid ABC transporter, permease protein
9344	phosphate ABC transporter, phosphate-binding protein (pstS)

9346	NOL1/NOP2/sun family protein (sun)
9348	Abortive infection protein family
9350	permease
9352	N-acetylmuramoyl-L-alanine amidase domain protein (usp45)
9354	ABC transporter, ATP-binding protein
9356	phosphoglucomutase (pgm)
9358	oxidoreductase, short chain dehydrogenase/reductase family
9360	phosphate acetyltransferase
9362	gls24 protein
9364	ribosomal protein S1 (rpsA)
9368	dTDP-glucose 4,6-dehydratase (rfbB)
9370	excinuclease ABC, C subunit (uvrC)
9372	MATE efflux family protein
9378	amino acid permease (rocE)
9380	DNA-binding response regulator TrcR (trcR)
9382	16S rRNA processing protein RimM (rimM)
9384	transcriptional regulator
9388	ribosomal protein L20 (rplT)
9394	sugar-binding transcriptional repressor, LacI family (malR)
9396	proton/peptide symporter family protein
9398	amino acid permease
9400	exoribonuclease, VacB/Rnb family (vacB)
9402	multi-drug resistance efflux pump (pmrA)
9404	adhesion lipoprotein (psaA)
9406	iron-dependent transcriptional regulator (sirR)
9410	branched-chain amino acid ABC transporter, amino acid-binding protein (
9412	amino acid permease
9414	SpoU rRNA Methylase family protein
9416	sodium/dicarboxylate symporter (gltP-2)
9418	branched-chain amino acid transport system II carrier protein (brnQ)
9420	alcohol dehydrogenase, zinc-containing
9422	aminotransferase, class I (aspB)
9424	ribosomal protein S6 (rpsF)
9426	A/G-specific adenine glycosylase (mutY)
9428	acid phosphatase (olpA)
9430	ribosomal protein S12 (rpsL)
9434	microcin immunity protein MccF (mccF-1)
9436	undecaprenyl diphosphate synthase (uppS)
9438	preprotein translocase, YajC subunit (yajC)
9440	chaperonin, 10 kDa (groES)
9444	YitT family protein
9446	serine protease (htrA)
9448	ribose-phosphate pyrophosphokinase (prsA)
9450	aromatic amino acid aminotransferase (araT)
9452	Recombination protein O (recO)
9454	Abortive infection protein family
9456	fatty acid/phospholipid synthesis protein PlsX (plsX)
9458	acyl carrier protein (acpP)
9462	phosphoribosylaminoimidazole carboxylase, ATPase subunit (purK)
9464	alcohol dehydrogenase, iron-containing
9466	ribosomal protein L18 (rplR)
9468	preprotein translocase, SecY subunit
9470	transcriptional regulator ComX1 (comX1)
9472	deoxyuridine 5`-triphosphate nucleotidohydrolase (dut)
9478	sugar-binding transcriptional regulator, LacI family (rbsR)
9480	SPFH domain/Band 7 family
9488	zinc ABC transporter, permease protein (adcB)
9492	abortive infection protein
9494	hydrolase, haloacid dehalogenase-like family

9496	response regulator (lytT)
9500	transketolase, C-terminal subunit
9502	polyribonucleotide nucleotidyltransferase (pnp)
9504	serine O-acetyltransferase (cysE)
9508	ribosomal protein L13 (rplM)
9510	replication initiation protein
9518	amino acid ABC transporter, amino acid-binding protein
9522	glycyl-tRNA synthetase, alpha subunit (glyQ)
9524	NADH oxidase
9528	transketolase (tkt)
9534	penicillin-binding protein 1A (pbp1A)
9536	cell division protein DivIVA (divIVA)
9538	sensor histidine kinase
9540	serine/threonine protein kinase (pknB)
9542	transcriptional regulator
9544	PTS system, IIA component (lacF)
9546	glycerol dehydrogenase (gldA)
9548	aspartate kinase (thrA)
9550	enoyl-CoA hydratase/isomerase family protein
9552	acyl carrier protein (acpP)
9564	ABC transporter, ATP-binding protein
9566	N utilization substance protein A (nusA)
9568	ribosome-binding factor A (rbfA)
9570	Cof family protein
9572	CoA binding domain protein (b0965)
9574	transcriptional regulator, Fur family
9578	queuine tRNA-ribosyltransferase (tgt)
9580	ribonuclease P protein component (rnpA)
9582	serine protease, subtilase family
9584	glycosyl transferase domain protein
9586	transcriptional activator, AraC family
9588	transcriptional regulator, TetR family
9590	transcriptional regulator, AraC family
9594	surface protein Rib
9596	transposase, mutator family
9600	acetyltransferase, GNAT family
9602	Transposase, Mutator family
9606	UDP-sugar hydrolase
9610	anthranilate synthase component II (trpG)
9612	biotin synthetase (bioB)
9616	UDP-N-acetylmuramoylalanine--D-glutamate ligase (murD)
9618	ylmF protein (ylmF)
9620	amino acid ABC transporter, permease protein
9622	phosphoglucomutase (pgm)
9624	YjeF-related protein, C-terminus
9626	FemAB family protein (fibA)
9628	Cof family protein
9630	cell division ABC transporter, permease protein FtsX (ftsX)
9632	oxidoreductase, short-chain dehydrogenase/reductase family (fabG)
9634	aspartate aminotransferase (aspC)
9638	ribosomal protein L31 (rpmE)
9640	nrdI protein (nrdI)
9642	ribosomal protein L19 (rplS)
9644	bacteriophage L54a, repressor protein
9646	bacteriophage L54a, antirepressor
9652	single-strand binding protein (ssb)
9660	pneumococcal surface protein A
9666	DNA-binding response regulator (vncR)
9668	transposase OrfAB, subunit B

9670	cell division protein, FtsW/RodA/SpoVE family (rodA)
9672	DNA gyrase, B subunit (gyrB)
9674	3-phosphoshikimate 1-carboxyvinyltransferase (aroA)
9676	RNA methyltransferase, TrmA family
9680	transcriptional regulator, AraC family
9682	ABC transporter, ATP-binding protein
9690	CylJ
9696	permease
9698	regulatory protein
9700	carbohydrate kinase, pfkB family
9702	beta-glucuronidase
9704	2-deydro-3-deoxyphosphogluconate aldolase/4-hydroxy-2-oxoglutarate aldo
9706	3-oxoacyl-(acyl-carrier-protein) reductase
9708	catabolite control protein A (ccpA)
9712	ribonuclease III (rnc)
9714	SMC family, C-terminal domain family
9718	S1 RNA binding domain protein
9722	prolipoprotein diacylglyceryl transferase (lgt)
9724	riboflavin synthase, alpha subunit (ribE)
9726	3,4-dihydroxy-2-butanone 4-phosphate synthase/GTP cyclohydrolase II (ri
9728	lysyl-tRNA synthetase (lysS)
9734	Transposase subfamily
9738	translation elongation factor Tu (tuf)
9740	UDP-N-acetylmuramoylalanyl-D-glutamyl-2,6-diaminopimelate--D-alanyl-D-a
9746	Glutathione S-transferases domain protein
9754	Ribonucleotide reductases
9756	biotin--acetyl-CoA-carboxylase ligase
9760	Uncharacterized protein family SNZ family
9762	methionine aminopeptidase, type I (map)
9764	DNA ligase, NAD-dependent (ligA)
9766	glucose-1-phosphate adenylyltransferase (glgC)
9768	UDP-N-acetylglucosamine 1-carboxyvinyltransferase (murA)
9770	acetyltransferase, GNAT family
9772	exonuclease RexA (rexA)
9774	tRNA modification GTPase TrmE (trmE)
9776	ABC transporter, ATP-binding protein
9778	pyruvate dehydrogenase complex, E1 component, pyruvate dehydrogenase al
9782	Mur ligase family protein
9786	HD domain protein
9788	translation elongation factor G (fusA)
9796	pyruvate kinase (pyk)
9798	Signal peptidase I
9802	cytidine deaminase (cdd)
9804	sugar ABC transporter, ATP-binding protein
9806	sugar ABC transporter, permease protein
9808	acetyltransferase, GNAT family
9810	ABC transporter, permease protein
9812	SatD
9814	Helix-turn-helix domain, fis-type protein
9816	phosphate ABC transporter, ATP-binding protein (pstB-1)
9818	tRNA pseudouridine synthase B (truB)
9820	Acetyltransferase (GNAT) family
9822	DNA topoisomerase I (topA)
9824	ribonuclease HII (rnhB)
9830	orotidine 5'-phosphate decarboxylase (pyrF)
9832	aspartate-semialdehyde dehydrogenase (asd)
9836	pantothenate metabolism flavoprotein (dfp)
9840	Sua5/YciO/YrdC/YwlC family protein
9844	thiamine biosynthesis protein ApbE

9846	Domain of unknown function
9848	DNA repair protein RadC (radC)
9850	glycosyl hydrolase, family 1 (bglA)
9852	Cof family protein (b0844)
9854	spermidine/putrescine ABC transporter, permease protein (potH)
9856	folylpolyglutamate synthase (folC)
9858	homoserine dehydrogenase (hom)
9860	succinate-semialdehyde dehydrogenase (gabD-1)
9862	membrane protein
9864	ATP-dependent DNA helicase PcrA (pcrA)
9866	uracil permease (uraA)
9868	sodiumalanine symporter family protein
9878	capsular polysaccharide biosynthesis protein Cps4B (cps4B)
9880	transcriptional regulator, LysR family
9882	CpslaS
9884	chloride channel protein
9886	tributyrin esterase (estA)
9888	ABC transporter, ATP-binding protein (potA)
9890	alpha-acetolactate decarboxylase (budA)
9892	TPR domain protein
9896	metallo-beta-lactamase superfamily protein
9898	tRNA delta(2)-isopentenylpyrophosphate transferase (miaA)
9902	glycerophosphoryl diester phosphodiesterase
9904	transposase OrfAB, subunit B
9906	IS3-Spn1, transposase
9908	transposase OrfAB, subunit B (orfB)
9910	reverse transcriptase
9916	transposase OrfAB, subunit B
9918	integrase, phage family (int)
9920	transcription regulator
9922	TnpA
9926	structural gene for ultraviolet resistance (uvra)
9930	Helicases conserved C-terminal domain protein
9932	abortive infection bacteriophage resistance protein (abiEi)
9944	ribosomal protein L7/L12 (rplL)
9948	ATP-dependent Clp protease, ATP-binding subunit ClpX (clpX)
9950	dihydrofolate reductase (folA)
9952	hemolysin
9954	transcriptional regulator, MarR family
9958	polyA polymerase family protein
9960	PTS system, fructose specific IIABC components (fruA-1)
9962	lactose phosphotransferase system repressor (lacR)
9964	choline binding protein D (cbpD)
9968	pyrimidine operon regulatory protein (pyrR)
9970	ribosomal large subunit pseudouridine synthase D (rluD)
9972	thiamine biosynthesis protein Thil (thil)
9974	3-dehydroquinate dehydratase, type I (aroD)
9976	iron compound ABC transporter, ATP-binding protein (fepC)
9980	transcriptional regulator
9982	glycosyl transferase domain protein
9984	Cps9H
9988	4-diphosphocytidyl-2C-methyl-D-erythritol synthase (ispD)
9990	licD1 protein (licD1)
9996	large conductance mechanosensitive channel protein (mscL)
10000	maltose ABC transporter, maltose-binding protein
10004	nucleotide sugar synthetase-like protein
10006	transcriptional regulator
10008	oxidoreductase, aldo/keto reductase family
10010	NAD(P)H-flavin oxidoreductase

10016	transcriptional regulator MutR
10018	GTP-binding protein Era (era)
10022	peptide methionine sulfoxide reductase (msrA)
10026	peptide ABC transporter, ATP-binding protein
10028	peptide ABC transporter, ATP-binding protein (amiE)
10030	peptide ABC transporter, peptide-binding protein
10032	transposase, IS30 family
10034	transcriptional regulator, LysR family
10036	spoE family protein (ftsK)
10044	methionyl-tRNA synthetase (metG)
10046	D-isomer specific 2-hydroxyacid dehydrogenase family protein (serA)
10048	acetyltransferase, GNAT family
10050	phosphoserine aminotransferase (serC)
10054	thymidylate kinase (tmk)
10060	branched-chain amino acid ABC transporter, permease protein (livH)
10062	ATP-dependent Clp protease, proteolytic subunit ClpP (clpP)
10064	uracil phosphoribosyltransferase (upp)
10066	potassium uptake protein, Trk family (trkH)
10068	glutamate racemase (murI)
10070	membrane protein
10072	HD domain protein
10074	Acylphosphatase
10076	spoIIIJ family protein
10078	acetyltransferase, GNAT family
10080	glucose-inhibited division protein B (gidB)
10082	potassium uptake protein, Trk family
10084	ABC transporter, permease protein
10088	isochorismatase family protein
10092	haloacid dehalogenase-like hydrolase superfamily
10094	membrane protein
10096	glutamyl-tRNA(Gln) amidotransferase, B subunit (gatB)
10098	CBS domain protein protein
10100	transcriptional regulator (codY)
10102	universal stress protein family
10104	L-asparaginase (ansA)
10106	oxidoreductase, aldo/keto reductase 2 family
10108	preprotein translocase, SecA subunit (secA)
10112	excinuclease ABC, A subunit (uvrA)
10114	magnesium transporter, CorA family (corA)
10116	thioredoxin (trx)
10118	MutS2 family protein (mutS2)
10122	DNA-damage inducible protein P (dinP)
10124	formate acetyltransferase (pfl)
10126	transcriptional regulator, Crp family
10128	transport ATP-binding protein CydC
10138	ribosomal-protein-alanine acetyltransferase (rimI)
10140	hydrolase
10144	D-alanine-activating enzyme (dltA)
10148	carbohydrate kinase, FGGY family
10150	transaldolase
10160	Helix-turn-helix domain protein
10164	single-strand binding protein (ssb)
10166	type II DNA modification methyltransferase Spn5252IP (spn5252IMP)
10174	integrase, phage family
10178	Cyclic nucleotide-binding domain protein
10180	transcriptional regulator, MarR family
10182	prolyl-tRNA synthetase (proS)
10184	leucine-rich protein
10186	lacX protein, truncation (lacX)

10188	tagatose-6-phosphate kinase (lacC)
10190	galactose-6-phosphate isomerase, LacB subunit (lacB)
10192	neuraminidase
10198	Histidine kinase-, DNA gyrase B-, phytochrome-like ATPase domain protei
10200	ABC transporter, ATP-binding protein
10202	PTS system, IIABC components (ptsG)
10204	phosphate regulon response regulator PhoB (phoB)
10212	Uncharacterized ACR, COG2161 subfamily
10216	abortive phage resistance protein
10222	TnpA
10226	acetyltransferase, GNAT family
10230	ABC transporter domain protein
10234	5-methyltetrahydropteroyltriglutamate--homocysteine methyltransferase (
10236	branched-chain amino acid transport protein AzlC (azlC)
10240	DNA-binding response regulator (srrA)
10242	leucyl-tRNA synthetase (leuS)
10246	NupC family protein
10248	transcriptional regulator, GntR family
10252	glyoxalase family protein
10254	anaerobic ribonucleoside-triphosphate reductase (nrdD)
10256	competence-induced protein Ccs4
10262	competence/damage-inducible protein CinA (cinA)
10264	DNA-3-methyladenine glycosylase I (tag)
10268	DNA mismatch repair protein HexB (hexB)
10270	arginine repressor (argR)
10272	arginyl-tRNA synthetase (argS)
10274	aspartyl-tRNA synthetase (aspS)
10276	histidyl-tRNA synthetase (hisS)
10280	AGR_pAT_51p
10286	hydrolase, alpha/beta hydrolase fold family
10288	phage infection protein
10290	Glucose inhibited division protein A (gidA)
10292	tRNA (5-methylaminomethyl-2-thiouridylate)-methyltransferase (trmU)
10296	arginine/ornithine antiporter (arcD)
10298	chromosomal replication initiator protein DnaA (dnaA)
10302	peptidyl-tRNA hydrolase (pth)
10310	phosphotyrosine protein phosphatase
10316	ribosomal protein L36 (rpmJ)
10318	ribosomal protein S13/S18 (rpsM)
10328	L-lactate dehydrogenase (ldh)
10330	ribosomal protein L28 (rpmB)
10362	RNA polymerase sigma-70 factor, ECF subfamily
10384	BioY family protein
10386	AtsA/ElaC family protein
10388	cytidine/deoxycytidylate deaminase family protein
10394	phosphorylase, Pnp/Udp family
10396	transcriptional regulator, MerR family
10402	methyltransferase (ubiE)
10412	type IV prepilin peptidase
10416	ylmG protein (ylmG)
10444	transposase OrfAB, subunit B
10446	IS150-like transposase
10452	Bacterial regulatory proteins, tetR family domain protein
10454	cell wall surface anchor family protein, authentic frameshift (clfB)
10456	transposase OrfAB, subunit A (orfA)
10460	chaperonin, 33 kDa (hslO)
10472	(3R)-hydroxymyristoyl-(acyl-carrier-protein) dehydratase (fabZ)
10482	sprT protein
10490	transcriptional regulator, MarR family

10498	transcriptional regulator
10504	glycogen biosynthesis protein GlgD (glgD)
10536	ribonucleoside-diphosphate reductase, alpha subunit, truncation (nrdD)
10538	LPXTG-motif cell wall anchor domain
10550	membrane protein
10554	arsenate reductase (arsC)
10564	transposase, authentic frameshift
10570	transposase OrfAB, subunit A (orfA)
10574	Tn5252, Orf 9 protein
10580	IS3-Spn1, transposase
10584	transcriptional regulator, ArsR family
10628	ribosomal protein L35 (rpmI)
10630	cytidylate kinase (cmk)
10636	MutT/nudix family protein
10644	preprotein translocase, SecG subunit
10680	ribosomal protein S18 (rpsR)
10682	single-strand binding protein (ssb)
10692	glyceraldehyde 3-phosphate dehydrogenase (gap)
10694	translation elongation factor G (fusA)
10696	ribosomal protein S7 (rpsG)
10704	phosphinothricin N-acetyltransferase (pat)
10730	nrdI protein (nrdI)
10732	accessory gene regulator protein C (blpH)
10744	rhodanese family protein (pspE)
10746	cAMP factor
10758	competence/damage-inducible protein CinA (cinA)
10770	transcriptional regulator, ArgR family (argR)
10772	FliP family family
10794	peptide ABC transporter, peptide-binding protein
10800	ribosomal protein S21 (rpsU)
10802	transposase, IS30 family
10816	mucin 2 precursor, intestinal
10854	SV40-transformed marker protein pG1-related protein
10856	SV40-transformed marker protein pG1-related protein
10858	SV40-transformed marker protein pG1-related protein
10860	SV40-transformed marker protein pG1-related protein
10862	SV40-transformed marker protein pG1-related protein
10864	SV40-transformed marker protein pG1-related protein
10866	SV40-transformed marker protein pG1-related protein
10910	transcriptional regulator
10920	ribosomal protein S11 (rpsK)
10922	elaA protein
10926	5-formyltetrahydrofolate cyclo-ligase family protein
10938	inositol monophosphatase family protein
10940	amino acid ABC transporter, amino acid-binding protein (artI)
10944	Holliday junction DNA helicase RuvB (ruvB)
10946	D-alanyl-D-alanine carboxypeptidase (dacA)
10948	lipoprotein (bmpD)
10950	peptidase, U32 family family
10952	protease maturation protein
10954	glutamyl-tRNA synthetase (gltX)
10956	GTP-binding protein LepA (lepA)
10960	translation initiation factor if-2
10962	phosphoenolpyruvate carboxylase (ppc)
10964	calcium E1-E2-type ATPase
10966	serine protease, subtilase family

CLAIMS

1. A protein comprising an amino acid sequence selected from the group consisting of SEQ IDs 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412, 414, 416, 418, 420, 422, 424, 426, 428, 430, 432, 434, 436, 438, 440, 442, 444, 446, 448, 450, 452, 454, 456, 458, 460, 462, 464, 466, 468, 470, 472, 474, 476, 478, 480, 482, 484, 486, 488, 490, 492, 494, 496, 498, 500, 502, 504, 506, 508, 510, 512, 514, 516, 518, 520, 522, 524, 526, 528, 530, 532, 534, 536, 538, 540, 542, 544, 546, 548, 550, 552, 554, 556, 558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594, 596, 598, 600, 602, 604, 606, 608, 610, 612, 614, 616, 618, 620, 622, 624, 626, 628, 630, 632, 634, 636, 638, 640, 642, 644, 646, 648, 650, 652, 654, 656, 658, 660, 662, 664, 666, 668, 670, 672, 674, 676, 678, 680, 682, 684, 686, 688, 690, 692, 694, 696, 698, 700, 702, 704, 706, 708, 710, 712, 714, 716, 718, 720, 722, 724, 726, 728, 730, 732, 734, 736, 738, 740, 742, 744, 746, 748, 750, 752, 754, 756, 758, 760, 762, 764, 766, 768, 770, 772, 774, 776, 778, 780, 782, 784, 786, 788, 790, 792, 794, 796, 798, 800, 802, 804, 806, 808, 810, 812, 814, 816, 818, 820, 822, 824, 826, 828, 830, 832, 834, 836, 838, 840, 842, 844, 846, 848, 850, 852, 854, 856, 858, 860, 862, 864, 866, 868, 870, 872, 874, 876, 878, 880, 882, 884, 886, 888, 890, 892, 894, 896, 898, 900, 902, 904, 906, 908, 910, 912, 914, 916, 918, 920, 922, 924, 926, 928, 930, 932, 934, 936, 938, 940, 942, 944, 946, 948, 950, 952, 954, 956, 958, 960, 962, 964, 966, 968, 970, 972, 974, 976, 978, 980, 982, 984, 986, 988, 990, 992, 994, 996, 998, 1000, 1002, 1004, 1006, 1008, 1010, 1012, 1014, 1016, 1018, 1020, 1022, 1024, 1026, 1028, 1030, 1032, 1034, 1036, 1038, 1040, 1042, 1044, 1046, 1048, 1050, 1052, 1054, 1056, 1058, 1060, 1062, 1064, 1066, 1068, 1070, 1072, 1074, 1076, 1078, 1080, 1082, 1084, 1086, 1088, 1090, 1092, 1094, 1096, 1098, 1100, 1102, 1104, 1106, 1108, 1110, 1112, 1114, 1116, 1118, 1120, 1122, 1124, 1126, 1128, 1130, 1132, 1134, 1136, 1138, 1140, 1142, 1144, 1146, 1148, 1150, 1152, 1154, 1156, 1158, 1160, 1162, 1164, 1166, 1168, 1170, 1172, 1174, 1176, 1178, 1180, 1182, 1184, 1186, 1188, 1190, 1192, 1194, 1196, 1198, 1200, 1202, 1204, 1206, 1208, 1210, 1212, 1214, 1216, 1218, 1220, 1222, 1224, 1226, 1228, 1230, 1232, 1234, 1236, 1238, 1240, 1242, 1244, 1246, 1248, 1250, 1252, 1254, 1256, 1258, 1260, 1262, 1264, 1266, 1268, 1270, 1272, 1274, 1276, 1278, 1280, 1282, 1284, 1286, 1288, 1290, 1292, 1294, 1296, 1298, 1300, 1302, 1304, 1306, 1308, 1310, 1312, 1314, 1316, 1318, 1320, 1322, 1324, 1326, 1328, 1330, 1332, 1334, 1336, 1338, 1340, 1342, 1344, 1346, 1348, 1350, 1352, 1354, 1356, 1358, 1360, 1362, 1364, 1366, 1368, 1370, 1372, 1374, 1376, 1378, 1380, 1382, 1384, 1386, 1388, 1390, 1392, 1394, 1396, 1398, 1400, 1402, 1404, 1406, 1408, 1410, 1412, 1414, 1416, 1418, 1420, 1422, 1424, 1426, 1428, 1430, 1432, 1434, 1436, 1438, 1440, 1442, 1444, 1446, 1448, 1450, 1452, 1454, 1456, 1458, 1460, 1462, 1464, 1466, 1468, 1470, 1472, 1474, 1476, 1478, 1480, 1482, 1484, 1486, 1488, 1490, 1492, 1494, 1496, 1498, 1500, 1502, 1504, 1506, 1508, 1510, 1512, 1514, 1516, 1518, 1520, 1522, 1524, 1526, 1528, 1530, 1532, 1534, 1536, 1538, 1540, 1542, 1544, 1546, 1548, 1550, 1552, 1554, 1556, 1558, 1560, 1562, 1564, 1566, 1568, 1570, 1572, 1574, 1576, 1578, 1580, 1582, 1584, 1586, 1588, 1590, 1592, 1594, 1596, 1598, 1600, 1602, 1604, 1606, 1608, 1610, 1612, 1614, 1616, 1618, 1620, 1622, 1624, 1626, 1628, 1630, 1632, 1634, 1636, 1638, 1640, 1642, 1644, 1646, 1648, 1650, 1652, 1654, 1656, 1658, 1660, 1662, 1664, 1666, 1668, 1670, 1672, 1674, 1676, 1678, 1680, 1682, 1684, 1686, 1688, 1690, 1692, 1694, 1696, 1698, 1700, 1702, 1704, 1706, 1708, 1710, 1712, 1714, 1716, 1718, 1720,

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2. A protein having 50% or greater sequence identity to a protein according to claim 1.

3. A protein comprising a fragment of 7 or more consecutive amino acids from an amino acid sequence selected from the group consisting of SEQ IDs 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412, 414, 416, 418, 420, 422, 424, 426, 428, 430, 432, 434, 436, 438, 440, 442, 444, 446, 448, 450, 452, 454, 456, 458, 460, 462, 464, 466, 468, 470, 472, 474, 476, 478, 480, 482, 484, 486, 488, 490, 492, 494, 496, 498, 500, 502, 504, 506, 508, 510, 512, 514, 516, 518, 520, 522, 524, 526, 528, 530, 532, 534, 536, 538, 540, 542, 544, 546, 548, 550, 552, 554, 556, 558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594, 596, 598, 600, 602, 604, 606, 608, 610, 612, 614, 616, 618, 620, 622, 624, 626, 628, 630, 632, 634, 636, 638, 640, 642, 644, 646, 648, 650, 652, 654, 656, 658, 660, 662, 664, 666, 668, 670, 672, 674, 676, 678, 680, 682, 684, 686, 688, 690, 692, 694, 696, 698, 700, 702, 704, 706, 708, 710, 712, 714, 716, 718, 720, 722, 724, 726, 728, 730, 732, 734, 736, 738, 740, 742, 744, 746, 748, 750, 752, 754, 756, 758, 760, 762, 764, 766, 768, 770, 772, 774, 776, 778, 780, 782, 784, 786, 788, 790, 792, 794, 796, 798, 800, 802, 804, 806, 808, 810, 812, 814, 816, 818, 820, 822, 824, 826, 828, 830, 832, 834, 836, 838, 840, 842, 844, 846, 848, 850, 852, 854, 856, 858, 860, 862, 864, 866, 868, 870, 872, 874, 876, 878, 880, 882, 884, 886, 888, 890, 892, 894, 896, 898, 900, 902, 904, 906, 908, 910, 912, 914, 916, 918, 920, 922, 924, 926, 928, 930, 932, 934, 936, 938, 940, 942, 944, 946, 948, 950, 952, 954, 956, 958, 960, 962, 964, 966, 968, 970, 972, 974, 976, 978, 980, 982, 984, 986, 988, 990, 992, 994, 996, 998, 1000, 1002, 1004, 1006, 1008, 1010, 1012, 1014, 1016, 1018, 1020, 1022, 1024, 1026, 1028, 1030, 1032, 1034, 1036, 1038, 1040, 1042, 1044, 1046, 1048, 1050, 1052, 1054, 1056, 1058, 1060, 1062, 1064, 1066, 1068, 1070, 1072, 1074, 1076, 1078, 1080, 1082, 1084, 1086, 1088, 1090, 1092, 1094, 1096, 1098, 1100, 1102, 1104, 1106, 1108, 1110, 1112, 1114, 1116, 1118, 1120, 1122, 1124, 1126, 1128, 1130, 1132, 1134, 1136, 1138, 1140, 1142, 1144, 1146, 1148, 1150, 1152, 1154, 1156, 1158, 1160, 1162, 1164, 1166, 1168, 1170, 1172, 1174, 1176, 1178, 1180, 1182, 1184, 1186, 1188, 1190, 1192, 1194, 1196, 1198, 1200, 1202, 1204, 1206, 1208, 1210, 1212, 1214, 1216, 1218, 1220, 1222, 1224, 1226, 1228, 1230, 1232, 1234, 1236, 1238, 1240, 1242, 1244, 1246, 1248, 1250, 1252, 1254, 1256, 1258, 1260, 1262, 1264, 1266, 1268, 1270, 1272, 1274, 1276, 1278, 1280, 1282, 1284, 1286, 1288, 1290, 1292, 1294, 1296, 1298, 1300, 1302, 1304, 1306, 1308, 1310, 1312, 1314, 1316, 1318, 1320, 1322, 1324, 1326, 1328, 1330, 1332, 1334, 1336, 1338, 1340, 1342, 1344, 1346, 1348, 1350, 1352, 1354, 1356, 1358, 1360, 1362, 1364, 1366, 1368, 1370, 1372, 1374, 1376, 1378, 1380, 1382, 1384, 1386, 1388, 1390, 1392, 1394, 1396, 1398, 1400, 1402, 1404, 1406, 1408, 1410, 1412, 1414, 1416, 1418, 1420, 1422, 1424, 1426, 1428, 1430, 1432, 1434, 1436, 1438, 1440, 1442, 1444, 1446, 1448, 1450, 1452, 1454, 1456, 1458, 1460, 1462, 1464, 1466, 1468, 1470, 1472, 1474, 1476, 1478, 1480, 1482, 1484, 1486, 1488, 1490, 1492, 1494, 1496, 1498, 1500, 1502, 1504, 1506, 1508, 1510, 1512, 1514, 1516, 1518, 1520, 1522, 1524, 1526, 1528, 1530, 1532, 1534, 1536, 1538, 1540, 1542, 1544, 1546, 1548, 1550, 1552, 1554, 1556, 1558, 1560, 1562, 1564, 1566, 1568, 1570, 1572, 1574, 1576, 1578, 1580, 1582, 1584, 1586, 1588, 1590,

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4. An antibody which binds to a protein according to any one of claims 1 to 3.

5. The antibody of claim 4, wherein said antibody is a monoclonal antibody, a chimeric antibody, a humanised antibody, or a fully human antibody.

6. A nucleic acid molecule which encodes a protein according to any one of claims 1 to 3.

7. A nucleic acid molecule according to claim 6, comprising a nucleotide sequence selected from the group consisting of SEQ IDs 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 377, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, 399, 401, 403, 405, 407, 409, 411, 413, 415, 417, 419, 421, 423, 425, 427, 429, 431, 433, 435, 437, 439, 441, 443, 445, 447, 449, 451, 453, 455, 457, 459, 461, 463, 465, 467, 469, 471, 473, 475, 477, 479, 481, 483, 485, 487, 489, 491, 493, 495, 497, 499, 501, 503, 505, 507, 509, 511, 513, 515, 517, 519, 521, 523, 525, 527, 529, 531, 533, 535, 537, 539, 541, 543, 545, 547, 549, 551, 553, 555, 557, 559, 561, 563, 565, 567, 569, 571, 573, 575, 577, 579, 581, 583, 585, 587, 589, 591, 593, 595, 597, 599, 601, 603, 605, 607, 609, 611, 613, 615, 617, 619, 621, 623, 625, 627, 629, 631, 633, 635, 637, 639, 641, 643, 645, 647, 649, 651, 653, 655, 657, 659, 661, 663, 665, 667, 669, 671, 673, 675, 677, 679, 681, 683, 685, 687, 689, 691, 693, 695, 697, 699, 701, 703, 705, 707, 709, 711, 713, 715, 717, 719, 721, 723, 725, 727, 729, 731, 733, 735, 737, 739, 741, 743, 745, 747, 749, 751, 753, 755, 757, 759, 761, 763, 765, 767, 769, 771, 773, 775, 777, 779, 781, 783, 785, 787, 789, 791, 793, 795, 797, 799, 801, 803, 805, 807, 809, 811, 813, 815, 817, 819, 821, 823, 825, 827, 829, 831, 833, 835, 837, 839, 841, 843, 845, 847, 849, 851, 853, 855, 857, 859, 861, 863, 865, 867, 869, 871, 873, 875, 877, 879, 881, 883, 885, 887, 889, 891, 893, 895, 897, 899, 901, 903, 905, 907, 909, 911, 913, 915, 917, 919, 921, 923, 925, 927, 929, 931, 933, 935, 937, 939, 941, 943, 945, 947, 949, 951, 953, 955, 957, 959, 961, 963, 965, 967, 969, 971, 973, 975, 977, 979, 981, 983, 985, 987, 989, 991, 993, 995, 997, 999, 1001, 1003, 1005, 1007, 1009, 1011, 1013, 1015, 1017, 1019, 1021, 1023, 1025, 1027, 1029, 1031, 1033, 1035, 1037, 1039, 1041, 1043, 1045, 1047, 1049, 1051, 1053, 1055, 1057, 1059, 1061, 1063, 1065, 1067, 1069, 1071, 1073, 1075, 1077, 1079, 1081, 1083, 1085, 1087, 1089, 1091, 1093, 1095, 1097, 1099, 1101, 1103, 1105, 1107, 1109, 1111, 1113, 1115, 1117, 1119, 1121, 1123, 1125, 1127, 1129, 1131, 1133, 1135, 1137, 1139, 1141, 1143, 1145, 1147, 1149, 1151, 1153, 1155, 1157, 1159, 1161, 1163, 1165, 1167, 1169, 1171, 1173, 1175, 1177, 1179, 1181, 1183, 1185, 1187, 1189, 1191, 1193, 1195, 1197, 1199, 1201, 1203, 1205, 1207, 1209, 1211, 1213, 1215, 1217, 1219, 1221, 1223, 1225, 1227, 1229, 1231, 1233, 1235, 1237, 1239, 1241, 1243, 1245, 1247, 1249, 1251, 1253, 1255, 1257, 1259, 1261, 1263, 1265, 1267, 1269, 1271, 1273, 1275, 1277, 1279, 1281, 1283, 1285, 1287, 1289, 1291, 1293, 1295, 1297, 1299, 1301, 1303, 1305, 1307, 1309, 1311, 1313, 1315, 1317, 1319, 1321, 1323, 1325, 1327, 1329,

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8. A nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ IDs 10967, 10968, 10969, 10970, 10971, 10972, 10973, 10974, 10975, 10976, 10977, 10978, 10979, 10980, 10981, 10982, 10983, 10984, 10985, 10986, 10987, 10988, 10989, 10990, 10991, 10992, 10993, 10994, 10995, 10996, 10997, 10998, 10999, 11000, 11001, 11002, 11003, 11004, 11005, 11006, 11007, 11008, 11009, 11010, 11011, 11012, 11013, 11014, 11015, 11016, 11017, 11018, 11019, 11020, 11021, 11022, 11023, 11024, 11025, 11026, 11027, 11028, 11029, 11030, 11031, 11032, 11033, 11034, 11035, 11036, 11037, 11038, 11039, 11040, 11041, 11042, 11043, 11044, 11045, 11046, 11047, 11048, 11049, 11050, 11051, 11052, 11053, 11054, 11055, 11056, 11057, 11058, 11059, 11060, 11061, 11062, 11063, 11064, 11065, 11066, 11067, 11068, 11069, 11070, 11071, 11072, 11073, 11074, 11075, 11076, 11077, 11078, 11079, 11080, 11081, 11082, 11083, 11084, 11085, 11086, 11087, 11088, 11089, 11090, 11091, 11092, 11093, 11094, 11095, 11096, 11097, 11098, 11099, 11100, 11101, 11102, 11103, 11104, 11105, 11106, 11107, 11108, 11109, 11110, 11111, 11112, 11113, 11114, 11115, 11116, 11117, 11118, 11119, 11120, 11121, 11122, 11123, 11124, 11125, 11126, 11127, 11128, 11129, 11130, 11131, 11132, 11133, 11134, 11135, 11136, 11137, 11138, 11139, 11140, 11141, 11142, 11143, 11144, 11145, 11146, 11147, 11148, 11149, 11150, 11151, 11152, 11153, 11154, 11155, 11156, 11157, 11158, 11159, 11160, 11161, 11162, 11163, 11164, 11165, 11166, 11167, 11168, 11169, 11170, 11171, 11172, 11173, 11174, 11175, 11176, 11177, 11178, 11179, 11180, 11181, 11182, 11183, 11184, 11185, 11186, 11187, 11188, 11189, 11190, 11191, 11192, 11193, 11194, 11195, 11196, 11197, 11198, 11199, 11200, 11201, 11202, 11203, 11204, 11205, 11206, 11207, 11208, 11209, 11210, 11211, 11212, 11213, 11214, 11215, 11216, 11217, 11218, 11219, 11220, 11221, 11222, 11223, 11224, 11225, 11226, 11227, 11228, 11229, 11230, 11231, 11232, 11233, 11234, 11235, 11236, 11237, 11238, 11239, 11240, 11241, 11242, 11243, 11244, 11245, 11246, 11247, 11248, 11249, 11250, 11251, 11252, 11253, 11254, 11255, 11256, 11257, 11258, 11259, 11260, 11261, 11262, 11263, 11264, 11265, 11266, 11267, 11268, 11269, 11270, 11271, 11272, 11273, 11274, 11275, 11276, 11277, 11278, 11279, 11280, 11281, 11282, 11283, 11284, 11285, 11286, 11287, 11288, 11289, 11290, 11291, 11292, 11293, 11294, 11295, 11296, 11297, 11298, 11299, 11300, 11301, 11302, 11303, 11304, 11305, 11306, 11307, 11308, 11309, 11310, 11311, 11312, 11313, 11314, 11315, 11316, 11317, 11318, 11319, 11320, 11321, 11322, 11323, 11324, 11325, 11326, 11327, 11328, 11329, 11330, 11331, 11332, 11333, 11334, 11335, 11336, 11337, 11338, 11339, 11340, 11341, 11342, 11343, 11344, 11345, 11346, 11347, 11348, 11349, 11350, 11351, 11352, 11353, 11354, 11355, 11356, 11357, 11358, 11359, 11360, 11361, 11362, 11363, 11364, 11365, 11366, 11367, 11368, 11369, 11370, 11371, 11372, 11373, 11374, 11375, 11376, 11377, 11378, 11379, 11380, 11381, 11382, 11383, 11384,

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12009, 12010, 12011, 12012, 12013, 12014, 12015, 12016, 12017, 12018, 12019, 12020, 12021, 12022, 12023 and 12024.

9. A nucleic acid molecule comprising a fragment of 10 or more consecutive nucleotides from a nucleotide sequence selected from the group consisting of SEQ IDs 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 377, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, 399, 401, 403, 405, 407, 409, 411, 413, 415, 417, 419, 421, 423, 425, 427, 429, 431, 433, 435, 437, 439, 441, 443, 445, 447, 449, 451, 453, 455, 457, 459, 461, 463, 465, 467, 469, 471, 473, 475, 477, 479, 481, 483, 485, 487, 489, 491, 493, 495, 497, 499, 501, 503, 505, 507, 509, 511, 513, 515, 517, 519, 521, 523, 525, 527, 529, 531, 533, 535, 537, 539, 541, 543, 545, 547, 549, 551, 553, 555, 557, 559, 561, 563, 565, 567, 569, 571, 573, 575, 577, 579, 581, 583, 585, 587, 589, 591, 593, 595, 597, 599, 601, 603, 605, 607, 609, 611, 613, 615, 617, 619, 621, 623, 625, 627, 629, 631, 633, 635, 637, 639, 641, 643, 645, 647, 649, 651, 653, 655, 657, 659, 661, 663, 665, 667, 669, 671, 673, 675, 677, 679, 681, 683, 685, 687, 689, 691, 693, 695, 697, 699, 701, 703, 705, 707, 709, 711, 713, 715, 717, 719, 721, 723, 725, 727, 729, 731, 733, 735, 737, 739, 741, 743, 745, 747, 749, 751, 753, 755, 757, 759, 761, 763, 765, 767, 769, 771, 773, 775, 777, 779, 781, 783, 785, 787, 789, 791, 793, 795, 797, 799, 801, 803, 805, 807, 809, 811, 813, 815, 817, 819, 821, 823, 825, 827, 829, 831, 833, 835, 837, 839, 841, 843, 845, 847, 849, 851, 853, 855, 857, 859, 861, 863, 865, 867, 869, 871, 873, 875, 877, 879, 881, 883, 885, 887, 889, 891, 893, 895, 897, 899, 901, 903, 905, 907, 909, 911, 913, 915, 917, 919, 921, 923, 925, 927, 929, 931, 933, 935, 937, 939, 941, 943, 945, 947, 949, 951, 953, 955, 957, 959, 961, 963, 965, 967, 969, 971, 973, 975, 977, 979, 981, 983, 985, 987, 989, 991, 993, 995, 997, 999, 1001, 1003, 1005, 1007, 1009, 1011, 1013, 1015, 1017, 1019, 1021, 1023, 1025, 1027, 1029, 1031, 1033, 1035, 1037, 1039, 1041, 1043, 1045, 1047, 1049, 1051, 1053, 1055, 1057, 1059, 1061, 1063, 1065, 1067, 1069, 1071, 1073, 1075, 1077, 1079, 1081, 1083, 1085, 1087, 1089, 1091, 1093, 1095, 1097, 1099, 1101, 1103, 1105, 1107, 1109, 1111, 1113, 1115, 1117, 1119, 1121, 1123, 1125, 1127, 1129, 1131, 1133, 1135, 1137, 1139, 1141, 1143, 1145, 1147, 1149, 1151, 1153, 1155, 1157, 1159, 1161, 1163, 1165, 1167, 1169, 1171, 1173, 1175, 1177, 1179, 1181, 1183, 1185, 1187, 1189, 1191, 1193, 1195, 1197, 1199, 1201, 1203, 1205, 1207, 1209, 1211, 1213, 1215, 1217, 1219, 1221, 1223, 1225, 1227, 1229, 1231, 1233, 1235, 1237, 1239, 1241, 1243, 1245, 1247, 1249, 1251, 1253, 1255, 1257, 1259, 1261, 1263, 1265, 1267, 1269, 1271, 1273, 1275, 1277, 1279, 1281, 1283, 1285, 1287, 1289, 1291, 1293, 1295, 1297, 1299, 1301, 1303, 1305, 1307, 1309, 1311, 1313, 1315, 1317, 1319, 1321, 1323, 1325, 1327, 1329, 1331, 1333, 1335, 1337, 1339, 1341, 1343, 1345, 1347, 1349, 1351, 1353, 1355, 1357, 1359, 1361, 1363, 1365, 1367, 1369, 1371, 1373, 1375, 1377, 1379, 1381, 1383, 1385, 1387, 1389, 1391, 1393, 1395, 1397, 1399, 1401, 1403, 1405, 1407, 1409, 1411, 1413, 1415, 1417, 1419, 1421, 1423, 1425, 1427, 1429, 1431, 1433, 1435, 1437, 1439, 1441, 1443, 1445, 1447, 1449, 1451, 1453, 1455, 1457, 1459, 1461, 1463, 1465, 1467, 1469, 1471, 1473, 1475, 1477, 1479, 1481, 1483, 1485, 1487, 1489, 1491, 1493, 1495, 1497, 1499, 1501, 1503, 1505, 1507, 1509, 1511, 1513, 1515, 1517, 1519, 1521, 1523, 1525, 1527, 1529, 1531, 1533, 1535, 1537, 1539, 1541, 1543, 1545, 1547, 1549, 1551, 1553, 1555, 1557, 1559, 1561, 1563, 1565, 1567, 1569, 1571, 1573, 1575, 1577, 1579, 1581, 1583, 1585, 1587, 1589, 1591, 1593, 1595, 1597, 1599, 1601, 1603, 1605, 1607, 1609, 1611, 1613, 1615, 1617, 1619, 1621, 1623,

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10. A nucleic acid molecule comprising a nucleotide sequence complementary to a nucleic acid molecule according to any one of claims 6 to 9.

11. A nucleic acid molecule comprising a nucleotide sequences having 50% or greater sequence identity to a nucleic acid molecule according to any one of claims 6 to 10.

12. A nucleic acid molecule which can hybridise to a nucleic acid molecule according to any one of claims 6 to 11 under high stringency conditions.

13. A composition comprising a protein, a nucleic acid molecule, or an antibody according to any preceding claim.

14. A composition according to claim 13, being an immunogenic composition, a vaccine composition or a diagnostic composition.

15. A composition according to claim 13 or claim 14 for use as a pharmaceutical.

16. The use of a composition according to claim 13 in the manufacture of a medicament for the treatment or prevention of infection or disease caused by streptococcus bacteria, particularly *S.agalactiae* and *S.pyogenes*.

17. A method of treating a patient, comprising administering to the patient a therapeutically effective amount of the composition of claim 13.

18. A hybrid protein represented by the formula NH_2-A-[-X-L-]$_n$-B-COOH, wherein X is an amino acid sequence as defined in claim 1, L is an optional linker amino acid sequence, A is an optional N-terminal amino acid sequence, B is an optional C-terminal amino acid sequence, and n is an integer greater than 1.

19. A kit comprising primers for amplifying a template sequence contained within a *Streptococcus* nucleic acid sequence, the kit comprising a first primer and a second primer, wherein the first primer is substantially complementary to said template sequence and the second primer is substantially complementary to a complement of said template sequence, wherein the parts of said primers which have substantial complementarity define the termini of the template sequence to be amplified.

20. A kit comprising first and second single-stranded oligonucleotides which allow amplification of a Streptococcus template nucleic acid sequence contained in a single- or double-stranded nucleic acid (or mixture thereof), wherein: (a) the first oligonucleotide comprises a primer sequence which is substantially complementary to said template nucleic acid sequence; (b) the second oligonucleotide comprises a primer sequence which is substantially complementary to the complement of said template nucleic acid sequence; (c) the first oligonucleotide and/or the second oligonucleotide comprise(s) sequence which is not compementary to said template nucleic acid; and (d) said primer sequences define the termini of the template sequence to be amplified.

21. The kit of claim 20, wherein the non-complementary sequence(s) of (c) comprise a restriction site and/or a promoter sequence.

22. A computer-readable medium containing one or more of SEQ IDs 1 to 12024.

23. A process for detecting Streptococcus in a biological sample, comprising the step of contacting nucleic acid according to any of claims 6 to 12 with the biological sample under hybridising conditions.

24. The process of claim 23, wherein the process involves nucleic acid amplification.

25. A process for determining whether a compound binds to a protein according to claim 1, claim 2 or claim 3, comprising the step of contacting a test compound with a protein according to claim 1, claim 2 or claim 3 and determining whether the test compound binds to said protein.

26. A compound identified by the process of claim 25.

27. A composition comprising a protein according to claim 1, claim 2 or claim 3 and one or more of the following antigens:
- a protein antigen from *Helicobacter pylori*;
- a protein antigen from *N.meningitidis* serogroup B;
- an outer-membrane vesicle (OMV) preparation from *N.meningitidis* serogroup B;
- a saccharide antigen from N.meningitidis serogroup A, C, W135 and/or Y;
- a saccharide antigen from *Streptococcus pneumoniae*;
- an antigen from hepatitis A virus;
- an antigen from hepatitis B virus;
- an antigen from hepatitis C virus;
- an antigen from *Bordetella pertussis*;
- a diphtheria antigen;
- a tetanus antigen;
- a saccharide antigen from *Haemophilus influenzae* B.
- an antigen from N.gonorrhoeae;
- an antigen from *Chlamydia pneumoniae*;
- an antigen from *Chlamydia trachomatis*;
- an antigen from *Porphyromonas gingivalis*;
- polio antigen(s);
- rabies antigen(s);
- measles, mumps and/or rubella antigens;
- influenza antigen(s);
- an antigen from *Moraxella catarrhalis*; and/or
- an antigen from *Staphylococcus aureus*.

28. A composition comprising two or more proteins, wherein each protein is a protein according to claim 1, claim 2 or claim 3.

FIGURE 13

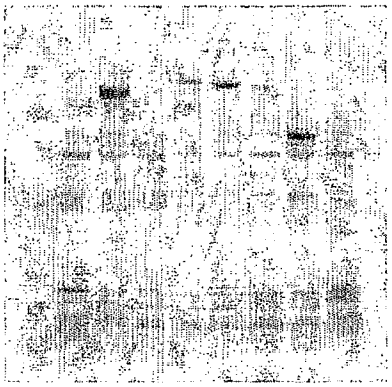


FIGURE 14

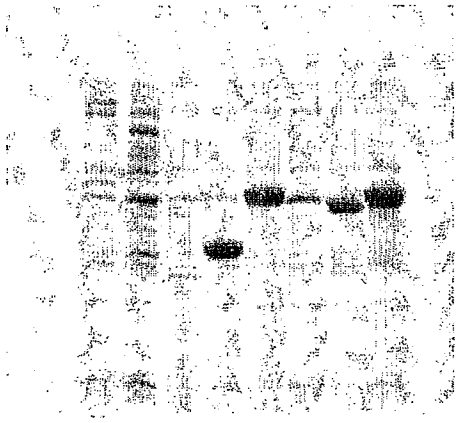


FIGURE 15

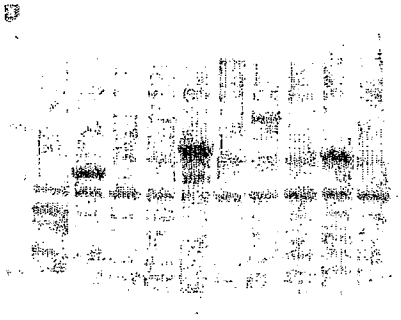


FIGURE 16

FIGURE 17

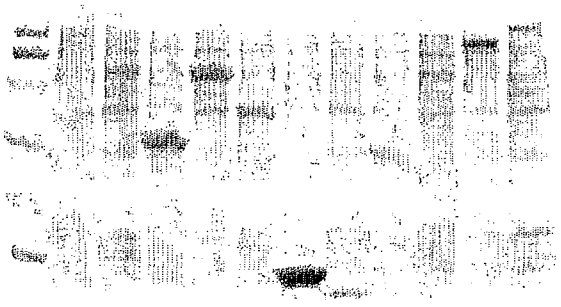


FIGURE 18

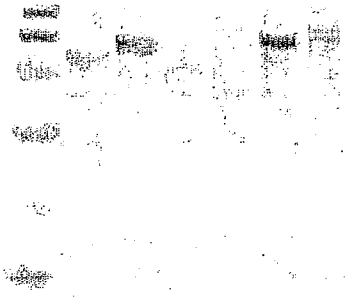


FIGURE 191

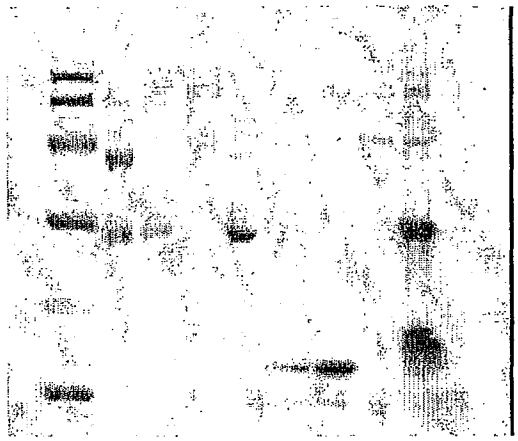


FIGURE 192

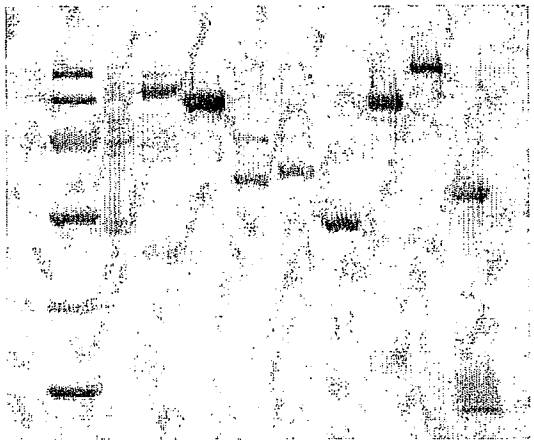
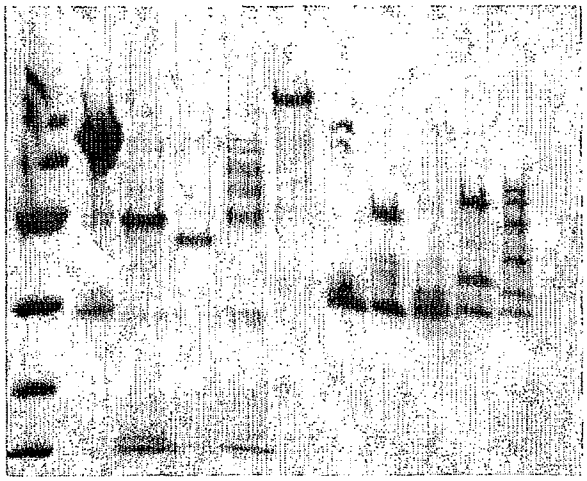


FIGURE 193



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SEQ ID 796

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